UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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CIRCULATORY SYSTEM DEVICES PANEL

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October 9, 2014
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, Maryland

PANEL MEMBERS:

RICHARD L. PAGE, M.D.	Panel Chair
RICHARD A. LANGE, M.D.	Voting Member
DAVID C. NAFTEL, Ph.D.	Voting Member
E. MAGNUS OHMAN, M.B., FRCPI, FACC	Voting Member
JOHN C. SOMBERG, M.D.	Voting Member
DAVID D. YUH, M.D.	Voting Member
RALPH BRINDIS, M.D.	Temporary Non-Voting Member
HUGH A. CASSIERE, M.D., FCCP	Temporary Non-Voting Member
JOAQUIN CIGARROA, M.D.	Temporary Non-Voting Member
JOHN R. DOTY, M.D.	Temporary Non-Voting Member
KAREN L. FURIE, M.D.	Temporary Non-Voting Member
JOHN W. HIRSHFELD, JR., M.D.	Temporary Non-Voting Member
RICHARD A. JONAS, M.D.	Temporary Non-Voting Member
DAVID E. KANDZARI, M.D.	Temporary Non-Voting Member
KRISTEN K. PATTON, M.D.	Temporary Non-Voting Member
DAVID J. SLOTWINER, M.D.	Temporary Non-Voting Member
CYNTHIA L. CHAUHAN, M.S.W.	Consumer Representative
DEBRA McCALL, B.S., M.A.M.	Patient Representative
NAVEEN THURAMALLA	Industry Representative
JAMIE MAE WATERHOUSE, M.B.A.	Designated Federal Officer

Free State Reporting, Inc.
1378 Cape St. Claire Road
Annapolis, MD 21409
(410) 974-0947

FDA REPRESENTATIVES:

BRAM D. ZUCKERMAN, M.D.
Director, Division of Cardiovascular Devices
Office of Device Evaluation

MARJORIE SHULMAN, M.B.A.
Director, Premarket Notification (510(k)) Program
Office of Device Evaluation

MORGAN LISCINSKY
Press Contact

FDA PRESENTERS:

DIANE NELL, Ph.D.
Division of Cardiovascular Devices
Office of Device Evaluation

STEVEN KURTZMAN, M.D.
Division of Cardiovascular Devices
Office of Device Evaluation

HELEN (HONGYING) JIANG, Ph.D.
Division of Epidemiology
Office of Surveillance and Biometrics

JENNY (CHIH-HSIN) LIU, RN, M.S.N.
Division of Postmarket Surveillance
Office of Surveillance and Biometrics

OPEN PUBLIC HEARING INDUSTRY SPEAKERS:

DAVID M. FRONK, M.S.
Vice President, Regulatory Affairs and Quality Assurance
CryoLife

WILLIAM F. NORTHRUP, III, M.D.
Vice President, Physician Relations and Education
CryoLife

SCOTT B. CAPPS, M.S.
Vice President, Clinical Research
CryoLife

RANDY PREBULA, J.D.
Hogan Lovells

GENERAL OPEN PUBLIC HEARING SPEAKERS:

JOHN W. BROWN, M.D.
Indiana University School of Medicine

RICHARD G. OHYE, M.D.
University of Michigan
C.S. Mott Children's Hospital
Congenital Heart Center

ALYCE JONES, Ph.D.
LifeNet Health

CHRISTINA SILCOX, Ph.D.
Senior Fellow
National Center for Health Research

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M E E T I N G

(8:02 a.m.)

DR. PAGE: Good morning. It's now 8:02, and I'd like to call this meeting of the Circulatory System Panel to order. My name is Dr. Richard Page. I'm Chair for this Panel. I'm a cardiac electrophysiologist, and I'm Chair of the Department of Medicine at the University of Wisconsin in Madison.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel participating in the meeting today has received training in FDA device law and regulations.

For today's agenda, the Panel will discuss and make recommendations regarding the classification of more-than-minimally manipulated allograft heart valves, or MMM allograft HVs.

Before we begin, I would like to ask our distinguished Panel and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation. I'll ask Dr. Zuckerman to start.

DR. ZUCKERMAN: Good morning. Bram Zuckerman, Director, FDA Division of Cardiovascular Devices.

DR. SLOTWINER: Good morning. David Slotwiner, cardiac electrophysiologist, North Shore-Long Island Jewish Health System, Hofstra University, New York.

DR. CIGARROA: Good morning. I'm Joaquin Cigarroa. I'm an interventional cardiologist and the Clinical Chief of the Knight Cardiovascular Institute at OHSU.

DR. OHMAN: Good morning. My name is Magnus Ohman. I'm a Professor of

Medicine at Duke, interventional cardiologist, expertise in clinical trials.

DR. JONAS: I'm Richard Jonas. I'm a congenital cardiac surgeon at Children's National Medical Center here in Washington, D.C.

DR. CASSIERE: Hugh Cassiere, Chief of Critical Care, Department of Cardiovascular and Thoracic Surgery, North Shore University Hospital.

DR. DOTY: John Doty, cardiovascular surgeon, Intermountain Medical Center, Salt Lake City, Utah.

DR. HIRSHFELD: I'm an interventional cardiologist at the University of Pennsylvania.

DR. YUH: Good morning. I'm David Yuh, Chief of Cardiac Surgery at Yale University. My areas of interest are in computational modeling of the heart and less invasive approaches to cardiac surgery.

DR. LANGE: My name is Rick Lange. My background is an interventional cardiologist, and incredulous as it seems, I'm actually President of the Texas Tech University Health Science Center in El Paso.

MS. WATERHOUSE: Jamie Waterhouse. I'm the Designated Federal Officer for the FDA.

DR. FURIE: Good morning. I'm Karen Furie, Chair of Neurology at the Alpert Medical School of Brown University.

DR. BRINDIS: Ralph Brindis, cardiologist, Professor of Medicine, UCSF Institute for Health Policy Studies and expertise in registries and outcomes research.

DR. NAFTEL: Good morning. I'm David Naftel. I'm Professor of Surgery and Professor of Biostatistics at the University of Alabama at Birmingham, and my area is

statistics.

DR. KANDZARI: Good morning. I'm David Kandzari. I am the Director of Interventional Cardiology and the Chief Scientific Officer at the Piedmont Heart Institute in Atlanta, Georgia.

DR. PATTON: Good morning. I'm Kristen Patton. I'm a cardiac electrophysiologist from University of Washington.

DR. SOMBERG: And good morning. I'm John Somberg. I'm a Professor of Medicine and Pharmacology at Rush University in Chicago and a cardiologist.

MS. McCALL: Good morning. I'm Debra McCall. I'm the Patient Representative and a volunteer at StopAfib.org.

MS. CHAUHAN: Good morning. I'm Cynthia Chauhan, Consumer Representative.

MR. THURAMALLA: Good morning. I'm Naveen Thuramalla. I'm serving as the Industry Rep on this Panel. I'm the Vice President of Engineering and Clinical Studies at Transonic Systems in Ithaca, New York.

DR. PAGE: Thank you very much.

I'll remind the Panel that these microphones need to be turned on just while you're speaking, so please turn off when you're done speaking, and I will call on you by seeing you raise your hand, and you don't need to turn on your microphone until you're actually given the opportunity to speak. This helps the acoustics for all of us.

We have a very impressive group and are undertaking an important job today. I do want to record all conversations in the minutes and the transcript, so as such, I'll ask for each Panelist to maintain our conversation just to the microphone and not between

ourselves during the Panel. And, obviously, we will not discuss the meeting at hand during breaks.

The other thing I'll mention is that I'm going to be watching the time very closely for each speaker to try to keep us on time so we can get the important work that we need to accomplish today done in a timely fashion.

I'd remind everyone in the room that if you have not already done so, please sign the attendance sheets that are on the tables by the doors.

Ms. Waterhouse, the Designated Federal Officer for the Circulatory Systems Device Panel, will now make some introductory remarks.

Ms. Waterhouse?

MS. WATERHOUSE: Good morning. I will now read the Conflict of Interest and Deputization Statements.

The Food and Drug Administration is convening today's meeting of the Circulatory System Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the Industry Representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S. Code Section 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance

with Federal ethics and conflict of interest laws. Under 18 U.S. Code Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussions of today's meeting, members and consultants of this Panel who are special Government employees or regular Federal employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S. Code Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss and make recommendations regarding the classification of more-than-minimally manipulated allograft heart valves. An MMM allograft heart valve is a human valve or valve conduit that has been aseptically recovered from qualified donors, dissected free from the human heart, and then subjected to a manufacturing processes that alters the original relevant characteristics of the tissue. FDA is seeking committee input on the safety and effectiveness of MMM allograft heart valves and the regulatory classification for MMM allograft heart valves. These valves are indicated for the replacement of diseased, damaged, malformed, or malfunctioning native or prosthetic valves.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in

accordance with 18 U.S. Code Section 208.

Naveen Thuramalla is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Transonic Systems.

We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firms at issue.

A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

For the duration of the Circulatory System Devices Panel meeting on October 9th, 2014, Ms. Debra McCall has been appointed as a Temporary Non-Voting Patient Representative. For the record, Ms. McCall serves as a patient representative to the Cardiovascular and Renal Drugs Advisory Committee in the Center for Drug Evaluation and Research. This individual is a special Government employee who has undergone the customary conflict of interest review and has reviewed the material to be considered at this meeting.

The appointment was authorized by Jill Hartzler Warner, J.D., Acting Associate Commissioner for Special Medical Programs, on October 2nd, 2014.

Before I turn the meeting back over to Dr. Page, I would like to make a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting, Incorporated. Their telephone number is 410-974-0947.

Information on purchasing videos of today's meeting and handouts for today's presentations are available at the registration table outside the meeting room.

The press contact for today's meeting is Morgan Liscinsky.

I would like to remind everyone that members of the public and the press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until after the Panel meeting has concluded.

If you are presenting in the Open Public Hearing today and have not previously provided an electronic copy of your slide presentation to the FDA, please arrange to do so with Ms. AnnMarie Williams at the registration desk.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time that you speak.

Finally, please silence your cell phones and other electronic devices at this time.

Thank you very much.

Dr. Page?

DR. PAGE: Thank you.

We will now hear a brief reclassification presentation from the FDA. I'd like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

MS. SHULMAN: Good morning. My name is Marjorie Shulman, and I'm going to talk today about device classification. I'm Director of the 510(k) Program for the Food and Drug

Administration.

(Pause.)

MS. SHULMAN: Okay. We just want a little dramatic suspense building.

Okay. So what is the purpose of this Panel meeting? It's to provide input to the FDA on the classification of a preamendment unclassified device type and whether FDA should call for PMAs or classify the device into Class I or Class II.

So what is a preamendment device? It's a device that was introduced into interstate commerce prior to May 28th, 1976, the enactment date of the Medical Device Amendments. An unclassified device is a preamendment device that was not classified in the original classification proceedings. Therefore, no classification regulation currently exists for this device type.

What are the device classes? Classification is based on the controls necessary to mitigate the risks. So a device should be placed in the lowest class whose level of control provides reasonable assurance of safety and effectiveness. Class I are general controls. Class II are general and special controls. And Class III is premarket approval.

General controls include such things as prohibition against adulterated or misbranded devices, good manufacturing practices, registration of the manufacturing facilities, listing of the device types, recordkeeping, repair, replacement, refund, et cetera.

Special controls include performance standards, postmarket surveillance, patient registries, and development and dissemination of guidelines.

Class I is for devices for which general controls are sufficient to provide reasonable assurance of safety and effectiveness. Class I devices typically do not require premarket

review prior to being marketed. Also, Class I are devices that cannot be classified into Class III because they are not life sustaining, life supporting, of substantial importance in preventing impairment of public health, and do not present a potential unreasonable risk of illness or injury. It's also for devices that can't be classified into Class II because insufficient information exists to determine special controls to provide reasonable assurance of the safety and effectiveness.

So here are some examples of Class I devices: General cardiovascular surgical instruments, adhesive bandages, manual stethoscopes, and crutches.

Class II is for devices that cannot be classified in Class I because the general controls by themselves are insufficient to provide reasonable assurance of safety and effectiveness, and there is sufficient information to establish special controls to provide such assurance. Class II devices typically require premarket notification, also known as 510(k), submitted to the FDA prior to being marketed.

Some examples of Class II devices are blood pressure cuffs, percutaneous catheters, electronic stethoscopes, et cetera.

So special controls, how are they used? So, for an example, a PTCA catheter was reclassified from Class III, premarket approval, to Class II, special controls. FDA issued a special controls guidance document to mitigate the risks to health. It included such things as biocompatibility testing, bench testing, animal testing, sterility and shelf life, and labeling that included requirements such as warnings, precautions, adverse events, et cetera. These special controls, in combination with the general controls, provided reasonable assurance of safety and effectiveness. Companies then have to provide evidence in their 510(k)

submission of how the special controls were addressed.

Class III is for devices that cannot be classified into Class II because insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness, and the devices are life sustaining and/or life supporting, or of substantial importance in preventing impairment of human health, or present unreasonable risk of illness or injury. Class III devices typically require premarket approval, also known as PMA, prior to being marketed.

So some examples of Class III devices: endovascular grafts, coronary and peripheral stents, percutaneous heart valves, LVADs, et cetera.

So the classification process consists of preamendment unclassified devices are classified after FDA has received a recommendation from a device classification panel, published the panel's recommendation for comment along with a proposed rule for classifying the device, and then published a final rule classifying the device.

So here is just a chart of the different classes and the paths it could go down. If general controls are sufficient, it could go to Class I; general and special, Class II; if they're not sufficient, it can go to Class III. So that's just a chart for your information.

So what do we need today? We would like input on the classification of the device that's the subject of this Panel session. The input should include the identification of the risks to health, if any, presented by the device; whether the device is life sustaining, life supporting, or of substantial importance in preventing impairment to human health, or presents an unreasonable risk of illness or injury; whether sufficient information exists to develop special controls; the identification of such special controls.

After the Panel meeting, FDA will consider the available evidence, including input of this Panel and public comments. FDA will issue a proposed rule classifying the device and seeking public comment. FDA will issue a final rule identifying the appropriate class. If Class II, devices may continue to be marketed. If Class III, FDA will issue a separate call for PMAs. If that's the case, existing devices will remain on the market until the submission of a PMA by a specified time, and they're allowed to continue to market. If the PMA device is not approved, devices will be considered misbranded and removed from commercial distribution.

Thank you.

DR. PAGE: Thanks very much.

Before I open this segment to questions from the Panel, could you show us slide 9 again? I'm confused by the second bullet, and I wonder whether that's a misprint. The second bullet for a Class I, insufficient information exists to establish special controls. There's no discussion of special controls for Class I, and is that the way it's meant to read? It looks like that was pulled from the Class III device definition.

MS. SHULMAN: So are you talking the second bullet there?

DR. PAGE: The second bullet, yeah.

MS. SHULMAN: So it's the little-known part of the Class I regulation that there is insufficient information to establish that the general or special controls are sufficient. So that's for -- the second bullet is devices that can't be classified into Class II because insufficient information exists to determine that the special controls and general controls do not provide reasonable assurance of safety and effectiveness.

So I know this is the confusing part of Class I. And, so far, the only device I'm aware of we've put into Class I are tweezer-type epilators for removing hair. So we don't know a lot about the device, but it's kind of no harm, no foul, and we've put it into Class I.

DR. PAGE: Okay. Thank you. I think I understand.

I'll now ask the Panel if they have any questions for Ms. Shulman.

Dr. Somberg?

DR. SOMBERG: In the consideration of classification, is there any legislative guidance, because this is all a rubric that's been created by the legislature. So is there any legislative guidance or rulemaking guidance on the implications of the classification on innovation and least burdensomeness in corporate development?

MS. SHULMAN: So it is in the regulations that a device should be placed in the lowest class that will provide reasonable assurance of safety and effectiveness. And that being said, the lowest class to provide reasonable assurance of safety and effectiveness would be the least burdensome manner to have the 510(k) -- to have the device classified.

DR. PAGE: Any other questions?

(No response.)

DR. PAGE: With that, I thank you.

MS. SHULMAN: Thank you.

DR. PAGE: And we'll move on to the FDA presentation.

DR. NELL: Good morning, Panel members, industry representatives, and audience members. My name is Diane Nell, and I am a mechanical engineer and reviewer in the Office of Device Evaluation within CDRH. I and my colleagues will be presenting

information on behalf of the FDA to classify more-than-minimally manipulated, or MMM, allograft heart valves. We will ask the Panel to provide recommendations regarding the regulatory classification of MMM allograft heart valves. We greatly appreciate your time and input to this classification proceeding.

This morning we will be discussing several topics beginning with a general introduction and the purpose of this Panel meeting. We will then provide a brief overview of the regulation of replacement heart valves within FDA followed by a description of MMM allograft heart valves. The regulatory history of MMM allograft heart valves will then be presented along with the proposed classification followed by the clinical background, a summary of the systematic literature review, other literature reports, and the MAUDE search of reported adverse events associated with MMM allograft heart valves. Finally, we will summarize the risks to health as well as the proposed classification. Throughout the presentation, questions for the Panel will be highlighted for discussion later in this morning's session.

DR. PAGE: (Off microphone) Once we get this going -- make sure we have a -- without hesitation, that would be wonderful. And we have you on the clock, but we'll give you the time back.

DR. NELL: Thank you.

DR. PAGE: If you have a statement, please say it to the microphone, Dr. Somberg.

DR. LANGE: I think he was saying that the slide review should be a Class II and needs special controls.

(Laughter.)

DR. PAGE: Thank you, Dr. Lange.

DR. NELL: Along with myself, the FDA team members who will be presenting today include Dr. Steven Kurtzman, Dr. Helen Jiang, and Ms. Jenny Liu.

The purpose of this Panel meeting is to discuss the classification of MMM allograft heart valves, which are regulated as medical devices in CDRH for use in heart valve replacement procedures. Replacement heart valves replace malfunctioning native or prosthetic heart valves and are intended to perform the function of the heart's natural valves. The Panel will be asked to make recommendations regarding the regulatory classification of these currently unclassified devices.

By way of introduction, we begin with a brief overview of the various replacement heart valves presently regulated within the FDA. Replacement heart valves may be categorized into the following three general categories: allograft or human heart valves, prosthetic heart valves, and MMM allograft heart valves. Allograft heart valves are human tissues regulated under Section 361 of the PHS Act and the tissue rules. Prosthetic heart valves are regulated as devices in CDRH, and all are Class III PMA devices. MMM allograft heart valves are also regulated as devices in CDRH, but they are presently unclassified devices and are the subject of this classification Panel meeting.

An allograft heart valve device is a human heart valve or valve conduit that has been aseptically recovered from qualified donors, dissected free from the human heart, and then subjected to a manufacturing process or processes, which alters the original relevant characteristics of the tissue. The valve is then stored until needed by a recipient. Note that these are not sterilized devices. The CryoValve SG Pulmonary Human Heart Valve cleared

under K033484 is such an MMM allograft heart valve and will be discussed further in this slide presentation.

As each new technology for manufacturing allograft heart valves is developed, manufacturers will need to consider whether all the criteria for regulations solely under Section 361 are met. Such criteria include whether or not the tissue is minimally manipulated.

The processing of the MMM allograft heart valve is critical and has a global effect on the valve tissue and may impact the hydrodynamic performance, the structural integrity, the durability, and the immunogenicity of the valve. And the MMM processing methods can vary widely across manufacturers and can evolve over time.

MMM processing represents relatively novel technology with a developmental history of less than two decades, as compared to the more than six decades of history of non-MMM replacement heart valves. Consequently, well-established scientific methods are lacking in various areas. For instance, regarding decellularization, there are no standards or even well-established scientific methods to evaluate decellularization processes, to conduct in vitro evaluations, and/or to evaluate in vivo recellularization. Important safety and effectiveness concerns include incomplete or variable decellularization, limited in vivo recellularization, and extracellular matrix structural deterioration.

And the regulatory history of MMM allograft heart valves is even more limited, with only one cleared MMM allograft heart valve. To date, the FDA has cleared only one MMM allograft heart valves from one manufacturer, namely the CryoValve SG Pulmonary Human

Heart Valve, a decellularized human heart valve. The clearance was based on comparison to the preamendments non-MMM allograft heart valve, or the standard cryopreserved allograft heart valve, which was marketed in the U.S. before passage of the Medical Device Amendments on May 28, 1976. Note that as of May 25, 2005, allograft heart valves that meet all criteria for regulation as tissue products under Section 361 of the PHS Act are no longer regulated as devices in CDRH.

FDA proposes classification of MMM allograft heart valves into Class III because they are life-sustaining devices for which insufficient information exists to establish special controls to mitigate the known risks to health, and the known risks cannot be adequately controlled by general and special controls. The risks were identified through a systematic literature review, and a medical device report, MDR, search and will be presented further in this slide presentation. It is worthy to note that the risks to health are consistent with other non-allograft replacement heart valves, all of which are regulated within CDRH as Class III devices.

A representative version of the indications for use for these devices is as follows: The device is indicated for the replacement of diseased, damaged, malformed, or malfunctioning native or prosthetic valves.

At this time, I would like to present Dr. Steven Kurtzman, who will present the clinical background pertaining to MMM allograft heart valves.

DR. KURTZMAN: Good morning. My name is Dr. Steven Kurtzman, and I will be presenting the clinical background pertaining to MMM allograft heart valves. I am a cardiologist in the Division of Cardiovascular Devices within CDRH.

It is estimated that more than 5 million Americans are diagnosed with heart valve disease each year. The prevalence of heart valve disease varies across the four valve positions, with aortic and mitral valve disease being the most prevalent.

Treatment options for malfunctioning heart valves include medical management, surgical or transcatheter valve repair, surgical replacement with any of numerous prosthetic heart valves or with an autograft valve from another valve position, or implantation of a transcatheter prosthetic heart valve.

Heart valves are replaced through open-heart surgery. Traditional surgical technique involves a full sternotomy along the full length of the breastbone. Newer, less invasive techniques include mini-sternotomy involving a smaller sternal incision and mini-thoracotomy through the ribcage. The patient is placed under general anesthesia and cardiopulmonary bypass. The surgery is typically 3 to 6 hours long. The surgery and recovery typically involve 3 to 10 days in the hospital and a recovery of 1 to 8 weeks at home, depending on the type of procedures, followed by 12 weeks of outpatient cardiac rehabilitation.

Allografts are mostly used in young patients with complex heart disease. In this population, they offer an advantage over porcine bioprosthetic valves, which have a high rate of structural valve dysfunction due to accelerated calcification, and an advantage over mechanical valves, which require anticoagulation. Additionally, allografts are available in smaller sizes than prosthetic heart valves. Allografts are also used in younger adults and less often used in older adults.

Pulmonary allograft valves are typically used either for right ventricular outflow tract

reconstruction or for the Ross Procedure to replace the pulmonary autograft used for aortic valve replacement. Aortic allograft valves are implanted less frequently than pulmonary allograft valves. It is estimated that less than 2,000 allografts or less are implanted per year in the United States.

As you will see in the following slide presentation from Dr. Jiang, our latest research has confirmed that the risks to health for MMM allograft heart valves based on literature reports of the one cleared CryoValve SG allograft heart valve are similar to those for non-allograft prosthetic heart valves except that MMM allografts have the added risk of immunogenicity and possibly increased infection since these are non-sterile devices.

At this time, I would like to present Dr. Helen Jiang, who will discuss the systematic literature review performed with the methods used.

DR. JIANG: Good morning, everyone. My name is Helen Jiang, an epidemiologist at Division of Epidemiology at CDRH/FDA. I will be presenting the results of the safety and effectiveness of the information from the literature on the use of MMM allograft heart valves.

To conduct the systematic literature review, we first used the following terms: allograft heart valves, CryoValve, or SynerGraft, because SynerGraft is the only cleared MMM allograft heart valve, to find all articles of the subject device. Then we add an additional search for homograft heart valves, as some articles have used homograft rather than allograft. The three major databases, PubMed, Embase, and Web of Science were searched within time limits from January 1990 to September 29th, 2014.

Here is a brief diagram showing how our final articles were selected. After our initial

search, a total of 241 articles were retrieved among which 204 were excluded. The number of excluded articles per exclusion criteria was listed on the top right dotted box. Then we further looked at the titles, abstracts, and full articles and further excluded another 16 articles based on the same exclusion criteria. This yield to a final of total 21 articles in our final review.

Here is a brief summary of the characteristics of all 21 articles. In terms of study design, there are no random control trials, but 10 prospective and 11 retrospective cohort studies. The study populations included infants to 80 years old of patients. There are 12 studies conducted in U.S. and 9 conducted outside U.S. Among those conducted within the U.S., five to six articles were funded by CryoLife. Valves were placed either at pulmonary position in 13 articles or at both pulmonary and aortic positions in seven articles, and at the aortic position only in one article. The focus of this literature review was on the 11 articles that include both SG and SA valves and 3 articles with SG valves only.

For the 13 SG studies that used SG devices, the sample size was ranged from 11 to 342 patients, and the follow-up times varied. The mean and median follow-up time by year ranged from half-year to 5.7 years. Maximum follow-up time reached 10 years post-implant.

The results of those 14 studies were summarized here. Among those reporting, the following safety endpoints were reported: Death or a valve-related death were ranged from 0 to 15%. Zero means that no deaths was found at the end of the study follow-up time. And the same notation was used for other endpoints. Endocarditis or infection was ranged from 0 to 2%. Thromboembolism, thrombus, or bleeding was ranged from 0 to 1%.

Re-intervention or re-operation was ranged from 4 to 19%. Valve or conduit deterioration and/or dysfunction was ranged from 0 to 26%. Calcification was ranged from 0 to 26%. Explant was listed separately in some studies, and it was ranged from 2 to 19%. Fibroproliferation was only reported in one study, and it was 42% at 10 months follow-up.

The effectiveness was presented in three aspects. Firstly, over variable follow-up times, pulmonary mean and peak pressure gradients increased in four articles. Two of them were probably clinically significant, and two of them are not clinically significant. Secondly, pulmonary effective orifice area, EOA, data was noted in one article, and it demonstrated a mild decrease over 6 months, which was not clinically significant. Thirdly, pulmonary valve regurgitation did not change clinically significantly or did not occur at up to 5 years follow-up in three studies.

Immune responses were also reported in eight studies. Overall, the immune response maintained low, that is, less than 10% positive to the immune test at up to 12 months follow-up.

The above-presented findings must be considered in light of the following key limitations in study design and methodology. First of all, there is a potential conflict of interest that is among nine U.S. studies. 67% of them were funded by the same company, CryoLife, either fully, partially, or possible. Secondly, sample sizes are small, especially 71% of the articles had less than 50 patients for the SG device, although we do need to keep in mind the -- usage of the device is limited per annual implants nationwide. Thirdly, generalization of immunology findings is challenging due to variations in valve positions, patient populations, and different detection techniques.

This ends my presentation. At this time, I would like to present Dr. Diane Nell again, who will present other reports on other MMM products.

DR. NELL: Good morning. My name is Diane Nell, and I will be summarizing reports on other decellularized products.

The published literature pertaining to MMM allograft heart valves is necessarily limited by the fact that only one such device has been 510(k) cleared. As such, a limited search was conducted for other decellularized products to determine if such reports might provide insights into additional potential risks not identified in the systematic literature review conducted for MMM allograft heart valves. Note that this was not a comprehensive search, but only a limited search to get a sense for additional potential risks that might have occurred as a result of decellularization.

Reports were found for the following products: A decellularized porcine heart valve, a decellularized femoral vein allograft, and a decellularized bovine femoral-posterior tibial bypass graft. Note that these devices are not cleared in the U.S. As such, there are no MDR reports. The safety concerns raised in these isolated reports are summarized in the following slides.

Simon reported on the rapid degeneration of a decellularized porcine heart valve implanted in four children, where failure occurred within 1 year. All four valves showed severe inflammation. Analyses of pre-implant valves revealed incomplete decellularization and calcific deposits.

Madden reported on a comparison of decellularized femoral vein allografts and prosthetic grafts for hemodialysis access. This was a prospective randomized study which

enrolled 27 patients in each arm. The study found significantly more access graft failures in the decellularized cohort versus the control.

Sharp reported a case study of a 68-year-old patient who experienced aneurysmal degeneration along the course of a decellularized bovine ureter used as a femoral-posterial tibial bypass graft.

And Stam reported that in decellularized porcine aortic valves, cell removal exposed the bare collagen fibers and increased the thrombogenicity of the valve.

It is not our intent to assert that decellularization was the cause of these reported failures because these are not devices that have been reviewed by the FDA, and the information in the reports are too limited to draw such conclusions. We presented these reports to merely highlight the concern that decellularization might have been a contributing factor in the failures and to illustrate that MMM processing has the potential to globally impact the structural integrity of the tissue. This therefore raises the concern that MMM allografts may present an increased risk of structural valve deterioration and aneurysmal degeneration as compared with standard cryopreserved allografts. Additionally, such processing may also present an increased risk of thrombus, thromboembolism, stroke, and renal insufficiency or failure as compared with standard cryopreserved allografts.

At this time, I would like to present Jenny Liu, who will discuss the MAUDE search conducted to identify the risks associated with MMM allograft heart valves.

MS. LIU: Good morning. My name is Jenny Chih-hsin Liu. I'm a nurse consultant in Office of Surveillance and Biometrics, CDRH/FDA. I will present the results of MAUDE

database search of medical device reports adverse event data for CryoValve SynerGraft Pulmonary Heart Valve. This is the only cleared MMM heart valve cleared.

The MAUDE database is the FDA database collecting postmarket adverse event information reported in the MDR. The MDR system has strengths and limitations. The strengths are the system provides a qualitative snapshot for adverse events for a specific device or device group in a real-world environment. It is a tool for signal detection or device problem and identification of rare, unexpected, or long-term event, and finally, characterization of the event in vulnerable patient population or off-label use or use error.

The limitations of the system include underreporting. That may, in part, be due to the lack of user awareness, insufficient information, inability to attribute a causality, and reporting bias, lack of a denominator data or usage data of the device. Therefore, the limitation resulted in inability to calculate the rate of adverse events and the data trend should be interpreted cautiously.

FDA conducted a query of the MAUDE database to assess the number and the type of the event for the CryoValve SynerGraft Allograft Pulmonary Valve, which is the only MMM allograft heart valve that has been cleared by the CDRH. Additionally, the database search also include the SynerGraft Aortic Heart Valve.

The search results were restricted by the end date, up to and including September 28th, 2014, and utilized the parameter of manufacturer name, brand name, catalogue and model number. The query resulted in the identification of 60 MDR on SynerGraft heart valves. Among those, two duplicate reports were excluded from the MDR dataset. Therefore, the following MDR analysis were based on 58 reports received in the

MAUDE database. Of the 58 reports, 31 were on SynerGraft Pulmonary Valve and 27 on aortic valve. We will discuss the pulmonary valve MDR first, including two death events in the following slide.

For the 31 MDR of SynerGraft Pulmonary Valve, the reported problem in the calculated time to the event occurrence (TTEO) value are listed in the table. The most frequently reported event for pulmonary valve was structural problem, 18 reports, followed by the infection/endocarditis, reaction, mass, incorrect size, and aneurysm. Of the 18 MDR noting structural problem, 17 provided TTEO values. Ten reports noted valve tissue tears, rips, holes, either after the thawing process prior to the device implant or within 1 day of implant surgery. The remaining seven reports noted structural problems identified beyond 1 day and up to 11 years post-implant.

Of the 18 reports of structural problems, two deaths were reported. One death was associated with the tear of the valve within 1 day post-implant. The other death was associated with the pulmonic stenosis and severe tricuspid regurgitation two months post-implant. The cause of the death for this case was not reported.

Of the seven infection/endocarditis events where the TTEO values were provided in the report, three events identified within 1 year of implantation, and the other two beyond 1 year.

The reported reaction, mass, aneurysm were observed within 1 year post-implant, while the problem of incorrect valve size was identified during the implant surgery.

Please note that some of the reported events, such as infection, endocarditis and aneurysm, are consistent with the event of -- the risk of other non-allograft heart valves

while other reported events, such as early structural problem, reaction, and mass might need further surveillance and/or additional data.

For the 27 MDR reported on SG Aortic Valve, the reported problem and the TTEO value are listed in this table. Of the 25 MDR cited structural problem, four events are identified the day of the implant surgery and two were identified between 1 day and 1 year. Some of the remaining 18 reports noting a structural problem may reflect the end of the life of the device. One report noted an infection, which was identified 2 weeks post-implant. There was a single event noting perioperative bleeding within 1 day of implant surgery.

In summary, the pulmonary and aortic valve for the -- these two valve, the MDR show the structural problem was the most frequently reported events. Of those events, a substantial proportion reflects the early structural problem which occurred within 1 year post-implant. There were two deaths associated with the structural problem of SG Pulmonary Heart Valve. The relationship between reaction and mass events and the SG Pulmonary Heart Valve remain unclear. Some events reported in MDR or MMM allograft heart valves were consistent with the risks of non-allograft heart valves while other events reported, such as early structural problem, reaction, mass, might warrant further surveillance and/or additional data.

This is the end of my presentation. Thank you.

And at this time, I would like to ask Dr. Diane Nell to come back to the podium. She will present a summary of the presentation along with the proposed classification for the MMM allograft heart valves. Thank you.

DR. NELL: Good morning. My name is Diane Nell, and I will be summarizing our

presentation thus far and presenting our proposed classification for MMM allograft heart valves.

Section 513(a)(1)(C) of the Act defines a Class III device as one for which insufficient information exists to determine that the application of general controls are sufficient to provide reasonable assurance of safety and effectiveness and for which insufficient information exists to determine that special controls would provide reasonable assurance of safety and effectiveness. In addition, the device is for use in sustaining human life or is one that presents a potential unreasonable risk of illness or injury.

FDA proposes classification of MMM allograft heart valves into Class III because they meet the criteria identified in the Act, as shown here. As mentioned, FDA believes that insufficient information exists to establish special controls for MMM allograft heart valves. Namely, only one MMM allograft heart valve has received clearance, and the history of literature pertaining to the device is limited, as previously presented.

Additionally, there are no standards to evaluate decellularization processes, to conduct in vitro performance evaluations of decellularized allograft valves, and/or to evaluate in vivo recellularization. For instance, as a class, MMM allograft heart valves could be subjected to various methods of decellularization. No one method has been established as the preferred method, and even for each method, there are no standardized protocols. The method for decellularization can impact the uniformity and consistency and the cellularity or the cellular debris that remains, and hence, the antigenicity of the finished product.

In addition, the method for quantification of the decellularization could also be

varied. Again, no one method has been established as the preferred method, nor are there standardized protocols. The type and accuracy of the quantification method is important to be able to monitor the process and to assess the impact of process changes. Beyond these standardized processes, there remain unanswered fundamental questions regarding decellularization processing and control, such as is the cellularity parameter that is being monitored clinically meaningful and how sensitive is the patient's immune response to the cellular debris that remains.

Given these limitations and the lack of standardized methods for processing and evaluation as well as the significant effect that processing may have on the product's safety and performance, FDA does not believe that special controls can be established to mitigate the known risks to health.

The Panel will be asked to address the sufficiency or lack thereof of information to establish special controls.

MMM allograft heart valves are life-sustaining devices because they replace malfunctioning native or prosthetic heart valves and are intended to perform the function of the heart's natural valves. The heart's valves control the flow of blood through the heart and are therefore critical to the life of the patient. It is estimated that more than 5 million Americans are diagnosed with heart valve disease each year, and MMM allograft heart valves are one treatment option.

FDA has identified a list of potential risks to health based on literature and the history of reported adverse events. A risk to health is a direct risk associated with the use of the device. An adverse event is a potential clinical consequence of the risk. For

example, structural valve deterioration may lead to death and thrombus could lead to stroke.

The risks to health and associated adverse events for MMM allograft heart valves are listed in this slide. The risks include structural valve deterioration, non-structural dysfunction, and others, as shown in the slide.

Particular risks due to the nature of MMM allograft heart valves and its processing include infection, since these are non-sterile devices. And, in addition, due to the novelty of MMM processing, isolated literature reports indicate the possibility of increased risks of structural valve deterioration, aneurysmal degeneration of any conduit portion, thrombus, thromboembolisms, stroke, and renal insufficiency or failure.

The Panel will be asked to address the completeness of the list of risks to health noted here.

The known risks cannot be adequately controlled by general and special controls because a full review of the methods used in and the facilities and controls used for the manufacturing and processing of MMM allograft heart valves is necessary to provide reasonable assurances of safety and effectiveness. The processing of the MMM allograft heart valves is critical and has a global effect on the valve tissue. Recall the device description, that the MMM allograft heart valve is one that has been subjected to processing, which alters the original relevant characteristics of the tissue. Thus, this processing will impact the hydrodynamic performance, structural integrity, durability, and immunogenicity of the valves. For these same reasons, the review of supplemental changes to the MMM processing is also necessary to provide reasonable assurances of

continued safety and effectiveness.

Generally, FDA considers manufacturing reviews to be a regulatory control reserved for Class III devices. This is because manufacturing reviews are outside of the regulatory authority of premarket notification submissions, which limits FDA's review of a 510(k) to the intended use and technology of the device. Consequently, due to the life-sustaining nature of MMM allograft heart valves, as well as the potential impact of MMM processing on valve safety and effectiveness, noting again that, by definition, such processing alters the original relevant characteristics of the tissue.

And due to the novelty and potential variability of MMM processing across manufacturers and over time, the FDA believes that the following controls are necessary to ensure the safety and effectiveness of MMM allograft heart valves: Premarket review of manufacturing information, pre-approval inspections, review of changes in manufacturing facility, location where finished devices are manufactured, postmarket review of significant manufacturing changes to ensure that the changes are adequately evaluated and tested prior to implementation, and annual reporting.

This table presents a summary of the regulatory requirements for three review paradigms, 510(k), 510(k) with special controls, and PMA. All three paradigms provide similar control regarding preclinical bench and animal studies. However, beyond that, the PMA paradigm provides increased control regarding clinical studies, premarket review of manufacturing procedures and facilities, as well as postmarket review of significant changes in manufacturing procedures and facilities. In addition, the PMA paradigm affords increased control regarding postmarket surveillance, including annual reporting and the

ability to require long-term post-approval studies. While the 510(k) or 510(k) with special controls paradigms include the optional control of 522 surveillance studies, those studies are generally limited to three years, which is often insufficient to assess the long-term performance of replacement heart valves, which are generally intended to function for 10 years or more. As such, due to the life-sustaining nature of replacement heart valves, the significant risks to health and the criticality of the MMM manufacturing process, the PMA paradigm provides the most appropriate level of regulatory control for MMM allograft heart valves.

Based on the safety and effectiveness information gathered by the FDA, we recommend that MMM allograft heart valves indicated for use in heart valve replacement procedures be regulated as Class III devices, requiring submission of a PMA to obtain marketing approval. It is worth noting once again that all other replacement heart valves regulated within CDRH are regulated as Class III PMA devices.

The Panel will be asked to comment on the classification recommendation for MMM allograft heart valves in heart valve replacement procedures.

Once again, a representative version of the indications for use for these devices is shown in this slide.

Thank you very much for your time and attention. This concludes the FDA presentation regarding the classification of MMM allograft heart valves. We are available to address any questions you might have at this time.

DR. PAGE: Thank you, Dr. Nell.

I'd like to thank the entire FDA group for their presentation.

Does anyone on the Panel have any brief clarifying question for the FDA? Please remember that the Panel may also ask the FDA questions during the Panel Deliberations later.

Dr. Somberg?

DR. SOMBERG: Yeah, I had a couple of questions, clarification. Is it my correct understanding of your statement that the non-MMM allograft valves were all PMA valves, evaluated by FDA at CBER as a PMA valve?

DR. NELL: The non-MMM allograft heart valves?

DR. SOMBERG: Yeah.

DR. NELL: Are regulated within CBER.

DR. SOMBERG: Okay.

DR. NELL: According to the tissue regs.

DR. SOMBERG: And they are evaluated as III or are they evaluated as a mixture?

DR. NELL: They're regulated as tissue products.

DR. SOMBERG: Do they have the same controls, then, as the PMA controls?

DR. NELL: They have --

DR. SOMBERG: Does CBER have those -- and I know it's different, the PMA and CBER is different than CDR, but how are there differences?

DR. NELL: So, generally -- sorry, I'm not an expert in CBER and how they regulate tissue products, but it's my understand that they are very much focused on donor eligibility and screening and those types of --

DR. SOMBERG: Yeah, but I'm talking about the controls that you were concerned

about that are missing for the MMM allograft valves that would be afforded under the PMA. Are those controls applied to the allograft, non-MMM valves as well?

DR. NELL: So I'm not sure --

DR. SOMBERG: Maybe you can get back to us later and --

DR. NELL: Yeah, I don't --

DR. SOMBERG: -- give me some information.

Can I ask a follow-up question also? Is it possible later on for you to get some information from the MAUDE database on the MDRs for the allograft, non-MMM? Because you show -- I mean, I always dislike data that doesn't have some comparative nature to it. Because you have two deaths, oh, two deaths. You have 18 of this or that. But it would be very helpful to know if this is not surprising for valves or this shows a signal that is disturbing in terms of durability, antigenicity, et cetera, et cetera. So is there comparative data on that, or is this just non-comparative information --

DR. ZUCKERMAN: So let's take a step back, Dr. Somberg. You've brought up two very important points. We will try to get more information, but this proceeding is different from our usual PMA single-device proceeding in that we don't have an extended lunch break to do that sort of homework.

But I do want to bring the Panel discussion back in context. You've inquired about CBER, or Center for Biologics regulation, which is an important issue. However, what is more important for this discussion is that MMM heart valves are regulated as a device in the Center for Devices. And the Panelists should be aware that all other heart valve devices regulated in the Center for Devices are PMA or Class III devices.

DR. SOMBERG: And I just have one --

DR. PAGE: Yes, Dr. Somberg?

DR. SOMBERG: -- one further -- and I apologize for leaving my mike on. It's hard to see the red thing when you're looking straight at it. I heard that there are less than 2,000 of these devices applied, and I wondered how one would factor in the HDE procedure. This could be a humanitarian drug exemption device. Would that still, if we changed the classification of classified to III, would that still apply to an HDE, because a manufacturer, given the volume exposed here, it's under 4,000. It would qualify as an HDE.

DR. ZUCKERMAN: Again, let's take a step back here. The purpose of this Panel discussion is to talk about an appropriate classification for the general class of devices known as MMM heart valves. Dr. Nell gave a specific example of one particular device which is presently available in the United States. But our goal today is not to dwell particularly on what would be the most efficient regulatory route for that particular device if our general regulatory strategy changes. Our goal today is to figure out what should be our general regulatory strategy. Once we have that in place, we always work with sponsors to figure out what is the so-called least burdensome and appropriate approach for regulation. Our goals here are to get good devices on the U.S. market. But we have a bigger picture challenge this morning, which refers to how do we figure out a regulatory strategy for a presently unclassified set of devices. So we need to concentrate on that global strategy. Thank you.

DR. PAGE: Thank you, Dr. Zuckerman.

Before I proceed to Dr. Kandzari, Dr. Yuh, and Dr. Cigarroa, whose hands I've seen

raised, I want to just expand on Dr. Somberg's comment. And Dr. Kurtzman's presentation slide 17 mentioned 2,000 allograft implants per year. Is that all allografts or is that MMM allografts?

DR. KURTZMAN: That's all allografts.

DR. PAGE: That's all allografts? And do you have any idea of what percentage of that 2,000 are MMM?

DR. KURTZMAN: No, I don't. I don't have that exact information.

DR. PAGE: Okay. Thank you.

Dr. Kandzari?

DR. KANDZARI: Well, on the heels of Dr. Page's comments, I have two questions, and the first will be abbreviated, then. Can you tell us how long this specific category has been commercially available in the United States, just to give us an estimate, because one of the limitations of MDR, of course, is that we never really know the true denominator, and so -- and it sounds like it's even more vague now that that's not -- this less than 2,000 is not that specific device. But how long has this been commercially available?

DR. NELL: Since 2008.

DR. KANDZARI: Thank you. Now, my second question is much different. And one of the concerns raised by FDA has been the immunogenicity related to the product. And in the literature search, there was a comment that immunogenicity represented less than 10% of the complications with this. But can someone please expand upon that further? Is immunogenicity meaning translation to endocarditis, or is there something else that you're concerned about, and how is that measured?

DR. NELL: So we listed immunogenicity as a potential risk because it is one that is associated with this device type. In considering the classification of these devices, we have to identify all of the potential risks. And this is indeed one of them. But it's not the only one. There are certainly concerns regarding the structural integrity and the durability because, again, this is, by definition, it's processing that's altering the tissue itself. It's actually physically changing the tissue, and there isn't a history of understanding what the impact is. I gave some examples, and I have other examples as well, of how the processing can affect the tissue and degrade it. So those are the concerns, but as a whole, and in considering our classification of the device, we have to consider all of the potential risks, and immunogenicity, being one of them, was listed.

DR. KANDZARI: Just to provide more detail, then, in that regard, I understand, broadly speaking, the concern of immunogenicity, but is it more specifically -- is that manifest as graft rejection or are you talking about just structural deterioration being a consequence of immunorejection for this? How do you mean specific to this technology?

DR. NELL: Yeah. I would be concerned with both, but I'll defer to Dr. Kurtzman, our clinical lead.

DR. KURTZMAN: The immunogenicity can refer to either structural valve dysfunction or rejection. You know, there is -- you know, that's our concern. There is, you know, there is different potential routes by which immunogenicity could lead to both. And --

DR. KANDZARI: Had true histologic evidence of rejection been reported in these documents? That did not seem to be clear.

DR. KURTZMAN: In the literature that we review -- go ahead, Dr. Jiang --

DR. JIANG: Hi, Helen Jiang from FDA for the systematic literature review. In those articles, eight articles that talk about immunogenicity, they normally just talk about the results for the test to the panel reaction antibodies, this HLA class, and there's no consequential clinical outcomes correlated with the result of this. And the follow-up time is short, only up to 1 year at max, most to 6 months.

DR. KANDZARI: Than you.

DR. PAGE: Thank you.

Dr. Yuh?

DR. YUH: Yeah, just a point of clarification. Can you just clarify why this valve would not be -- would not fall under CBER? Is it because of the decellularization technique imparted on this particular biologic? Is that the sole differentiating --

DR. NELL: Yeah. So what distinguishes what is regulated in CDRH, the Center for Devices, for CBER, the Center for Biologics, is whether or not the tissue is more than minimally manipulated. And for decellularization, decellularization in this case is determined to be more than minimal manipulation. So, if it is more than minimal manipulation to the tissue, then it's not regulated within CBER. It's regulated as a device within CDRH.

DR. YUH: So standard SA grafts, then, are considered minimally manipulated, but aren't they subject to, for example, different preservation techniques which might have almost a similar impact on the functioning of the graft?

DR. NELL: So there is a Tissue Reference Group that evaluates specific products and looks at how their processes and what their intended uses are, and they make the

determination of whether something is more than minimally manipulated or not, so whether it would be regulated under CBER or whether it would be regulated under CDRH. The TRG has determined that the more than minimally manipulated, decellularized allograft heart valves is a significant change and is a device to be regulated under CDRH.

DR. YUH: Okay. Thanks.

DR. PAGE: Dr. Cigarroa?

DR. CIGARROA: Similar point to Dr. Yuh, the issue of how special controls and regulations occur in the many different ways of crosslinking through glutaraldehyde, mediated ways on the tissue valves and their additional enhancements that can be done that can affect the tendency to calcify or not. But I think that's regulated by the other section, so I don't think that applies.

DR. PAGE: Right. I think you're correct. At this point, it's not in question whether this device is going to be under regulation from CDRH. That's a regulatory issue that's already been established and I don't think is being contested.

Yeah, Dr. Cigarroa?

DR. CIGARROA: It's interesting when one looks at how this -- I mean, in going back to the MAUDE database and how this device is being utilized specifically in the pulmonic position, many of these individuals, I suspect, are individuals with congenital heart disease. And so when one looks at the event rates, especially in individuals who are going through a second or third procedure, I think it becomes important to interpret that dataset in the context of the patients who are being treated. And the event rates, as we think about, in adult non-congenital patients who are undergoing aortic valve surgery or pulmonic valve

surgery, are distinctly different than in the congenital heart. And so knowing the types of patients that are reported in that MAUDE dataset is important to provide a set perspective.

DR. PAGE: Thank you.

Dr. Lange?

DR. LANGE: Again, just a clarification or question. I know that all the other valves that are used that are regulated under CDRH are Class III. Are there other bioprosthetic valves regulated by CDRH besides this valve?

DR. NELL: So, yes, CDRH regulates mechanical valves and bioprosthetic valves, and all of them are regulated as Class III PMA devices in CDRH.

DR. LANGE: Thank you.

DR. PAGE: Dr. Ohman?

DR. OHMAN: Yes. Thank you for the presentation. I'd like to go back to slides 24 and 25. I'm curious here, because this is actually sort of the groundwork. And it looks to me that we have data at least published on 600 patients of which you, if I understood your presentation correctly, you presented that there is about 2,000 of these procedures estimated carried out. And this is a fairly high publication rate. So I'm curious what's the average adverse events shown on the slide 25, maybe with some confidence intervals? I recognize Dr. Zuckerman has already pointed out we don't have a leisure of a lunch, but it is very helpful if the range for death is 15%, and that's out of the Brown study, bottom of the previous slide, that's worrisome, whereas if it's out of the first one with 11 patients, that's not so worrisome because that only represents one patient. So getting some average of these estimates would be very important to understand for us to be grounded in what we

are looking at.

DR. PAGE: Dr. Ohman, just so I understand, I don't know that a robust statistical analysis can be undertaken by the FDA today --

DR. OHMAN: No, I recognize that, and I --

DR. PAGE: But what you're asking for is, for example, what -- we saw a range of mortality from different studies, and you accurately point out that one study is fivefold larger than the next largest, and you're interested in a bit more granularity in terms of especially that larger study?

DR. OHMAN: Right, because we --

DR. PAGE: The Bechtel 2003?

DR. OHMAN: Yeah. Well, I just recognize that we need a better understanding of the overall assessment here rather than the individual studies that are -- some that are very, very small.

DR. PAGE: Why don't we ask FDA if that paper could be identified this morning? That would be helpful, but again, I don't want to get way off track. We're not here to evaluate necessarily this valve, but to discuss classification of a general class of device.

DR. ZUCKERMAN: Thank you, Dr. Page. A second question is: Can someone like Dr. Jonas, a pediatric heart surgeon, help us put slides 24 and 25 into better context?

DR. JONAS: Well, I think Dr. Cigarroa has already made the point that in the setting of congenital heart disease, it can be extremely difficult to come up with a reasonable mortality estimate unlike adult series, where one has the luxury of thousands of patients. We start off with a very diverse patient population that's also very small. So I think it's

really very difficult to look at series, small series like these, most of which have only 20 or 30 patients in them, and without knowing the specific details of the underlying congenital anomaly for which the implant was done come up with a reasonable estimate of what would be a reasonable mortality risk. So I think it's difficult to analyze mortality in these sorts of series.

DR. PAGE: Dr. Doty, did you have a comment?

DR. DOTY: I do. I just want to follow up what Dr. Jonas said. Even the adult cardiac surgery population using allograft valves are not a large series. So many of these patients that get these valves have specific indications, active endocarditis, pulmonic endocarditis, small aortic valve root size. So, again, you're not going to get the large data using these kind of valves. You just won't get randomized trials because the vast majority of patients that have aortic valve replacement in the adult population get some other type of valve.

DR. PAGE: Thank you for that clarification.

Dr. Patton?

DR. PATTON: I just wanted to ask the FDA: Is your goal in showing us this data for us to see that there are data that allow us to put this valve in the context of being similar to other valves that you regulate as opposed to we're -- my understanding is that we're not -- we don't really care that much about the details of this data because we're not evaluating this valve per se?

DR. NELL: Yes, yes.

DR. PATTON: Okay.

DR. NELL: That is correct. The purpose to presenting the information was it's

certainly relevant from the standpoint that we do have the one that is on the market that is a decellularized valve. So we need to present that information to you. But really in the context of what the risks are and not so much from the standpoint of its specific performance, because the performance is really irrelevant to the discussion here today, we're really needing to focus on what the risks are to health and whether those risks can be mitigated by special controls under 510(k) or whether they need to be addressed through the controls available under PMA.

DR. PAGE: Thank you.

Dr. Somberg?

DR. SOMBERG: In light of some of the comments of our surgical colleagues on the Panel today, I wonder -- and my summary or take on that was that these are going to be very small series and they are very heterogeneous populations that are looked at. In light of that information, I was curious to know what the FDA might envision a PMA? And the reason I'm asking this is I've always looked upon a PMA application as a critical part is the clinical studies. Dr. Nell, I think today you pointed out another aspect, which I never really registered in my head, that it's all the controls and the regulatory ability. So we may be talking at cross-purposes here. The FDA may be talking about having these extra ability to check manufacturing sites and changes in manufacturing procedures, and here I'm thinking about a nice randomized 5,000-patient placebo -- you know, not placebo, but positive control study or something like that. So we're talking at cross-purposes. So I would like to hear the -- and Dr. Zuckerman is going for the microphone, so maybe you can say what a PMA might entail, because it may entail really just sort of like a registry follow-up, but at

the same time, it might entail a very rigorous manufacturing and procedural controls.

DR. ZUCKERMAN: Okay. Dr. Somberg, you and others have been members of this Panel for a long time and recognize that the Center for Devices is obligated to work with a sponsor to develop a clinical trial strategy that, at the end of the day, can show a reasonable assurance of safety and effectiveness for Class III devices. However, there are no FDA regulations that state that for every Class III device, we need a randomized controlled trial, as you're implying. We have to look at the clinical context -- you know, it would be very important in a case like this where there are a limited number of valves implanted -- and develop an appropriate clinical trial strategy. As many of the cardiac surgeons know on this panel, the use of registries with performance goal or OPC data are a standard part of heart valve regulation except for the percutaneous heart valves, where there are quite a few implanted.

So I don't think that we particularly have to worry about the Agency and any sponsor developing an appropriate clinical trial stratagem as opposed to getting back to some of the basic points and questions that Dr. Nell has raised for this Panel, which revolve more about the global strategy and where in the scheme of things, the regulatory scheme of things, do MMM devices as a class sit.

DR. PAGE: Thank you, Dr. Zuckerman. And I think this is going to be a topic of some further discussion later on.

I'll ask for any other brief clarifying questions for the FDA, reminding the Panel that we will have another opportunity to ask them questions later in our discussion time.

Dr. Jonas, did you have another question?

DR. JONAS: Yes. I wanted to follow on from a point that Dr. Yuh had made. And, also, to remind everyone here that we are talking about a resource that is extremely limited. We are calling this a device, but this is donated human tissue, and in many cases donations from small children. And there is a great lack of this particular tissue. It can be extremely difficult for us to obtain valves of an appropriate size for children undergoing congenital heart surgery.

I'd really like to understand better why it is the FDA believes that the decellularization process might be more likely to be responsible for structural integrity problems rather than, for example, the amount of warm ischemic time after a valve is harvested, the amount of cold ischemic time, the dissection technique that's undertaken in preparing the valve, the particular mix of antibiotics that's selected by the company preparing the valve, and most importantly, the cryopreservation technique. You alluded, Ms. Nell, to 60 years of history with the standard allograft valve. I would point out that cryopreservation has only been used over the last 30 years and, in some ways, is still evolving. And there are various cryopreservation techniques that I think are frequently responsible for some of the issues that we've seen, such as cracking and structural failure. There is also the issue of thawing, how is a device handled once it gets to the operating room, how well is it stored in the operating room. Is it stored at the correct temperature, and does the operating team thaw and handle the device appropriate -- or the valve appropriately as it's being thawed and prepared in the operating room.

So I'm having trouble understanding why you're attributing these issues we're seeing in the MAUDE database to decellularization.

DR. NELL: So all of those issues that you raised are certainly relevant, and they're still relevant -- they're relevant to the non-MMM allograft valves that are regulated under CBER, and they would be relevant for those that are MMM-processed and regulated within CDRH, the difference being that the devices that are regulated within CDRH, our focus is, or our concern is with the MMM processing itself and what impact that might have on the tissue. I reported on one decellularized porcine valve which experienced accelerated degeneration, and some patients died as a result of the lack of structural integrity of that product. And that's where the concern is, is that there is so little known about decellularization and its impact on the tissue that we need to be concerned about how those products are actually processed and make sure that we have an understanding of the process and that we can evaluate it -- I can pull this up.

So this is just a backup slide. This is just a small sampling of some current reports, all of which were published this year, documenting research into various decellularization techniques and the impact on the tissue. And, again, there are many different techniques for decellularizing tissue, and none of them have any existing standards. Tsuchiya reports that the pH of the decellularization solution influences the extracellular matrix retention, cell removal, and also the potential for host response. Preservation of ECM components, including elastin, fibronectin, and laminin, were better retained in the lower pH conditions.

Xu reports that two methods of decellularization disturbed the structure of the annular fibrosis. All protocols maintained collagen content, but glycosaminoglycan content was lost to different degrees. And, furthermore, one method decreased the tensile mechanical property. And then Qu reports that despite the histological appearance of

vessel integrity, none of the flaps maintained physiologic vascular integrity.

And this is just a small sampling of some of the literature that's out there right now regarding decellularized products. Relatively speaking, decellularization is a relatively novel technology that is currently being developed. There are a lot of changes, and the impact to tissue is different depending on what the tissue is. So we have to be concerned with how they're actually manufacturing these tissues, which, by definition, the MMM tissues have been altered from their original relevant characteristics. And we have to be cognizant of what those alterations are and what the impact is going to be to the integrity and durability of the tissue once it's implanted.

DR. PAGE: Thank you for that very nice explanation.

I'm going to take the Chair's prerogative to call a break until 9:55, so a 15-minute break. I think what Dr. Nell just summarized for us is very helpful. We have -- I want to make sure we give plenty of time for the Industry Open Public Hearing, which is going to follow the break. And then we'll be able to discuss further -- we will be able to ask further questions of the FDA and others as we like.

But I think what was just summarized was very valuable in that we're not here to provide a specific recommendation with regard to a device. We're doing a different job here today. What was just pointed out was, independent of the safety and efficacy of the device that we're going to be discussing subsequently, we're here to determine whether MMM heart valves should be regulated as Class III devices when we recognize that the MMM can include multiple different manufacturing processes independent of or different from, and perhaps inferior to, the MMM that's being undertaken for the device we are

discussing today.

But, again, we're not here to adjudicate in terms of approval of that device. We're likely going to hear that it's a valuable device, and we will need to, as part of our work today, give guidance if this were to be labeled as a Class III device, how we can make sure that an important technology would be available. And as Dr. Zuckerman mentioned, we need to make sure that we understand what FDA calls the least burdensome regulatory process to allow the device to be available, if appropriate.

So, with that, I will ask us to take a 10-minute, a 15-minute break, and we'll reconvene at 9:55. I'll remind the Panel members not to discuss the matter at hand with anybody during the break.

Thank you.

(Off the record.)

(On the record.)

DR. PAGE: Will the Panelists please take their seats? We'll call ourselves back to order. It's now time to proceed with the Open Public Hearing portion of the meeting reserved for related industry. Excuse me.

Public attendees are giving an opportunity to address the Panel to present data, information, or views relevant to the meeting agenda. Ms. Waterhouse will now read the Open Public Hearing disclosure process statement.

MS. WATERHOUSE: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA

believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. PAGE: Thank you.

We'll now proceed with the -- we have one request to speak from CryoLife. The company will be given 30 minutes for their presentation.

Welcome.

MR. FRONK: Thank you. And good morning, Mr. Chairman. My name is Dave Fronk, and I am the Vice President of Regulatory Affairs and Quality Assurance for CryoLife, the manufacturer of the CryoValve SG Pulmonary Heart Valve, the FDA-cleared more-than-minimally manipulated allograft heart valve. On behalf of our company, I would like to thank the Panel members for the time and attention to addressing the Agency's request for input into the classification of these human tissue-sourced medical devices.

Before I begin, it is important to define some terminology that we will be using this morning. First, MM allograft heart valves. These are heart valves that are recovered from

screened donors and processed with minimal manipulation. CryoLife is a processor of MM allograft heart valves. These are regulated by CBER. They have manufacturing controls, which are referred to as good tissue practices. It is important to note that they are regulated without any form of premarket review.

MMM allograft heart valves are again recovered from screened donors and are processed with more-than-minimal manipulation. And as you heard this morning, more-than-minimal manipulation is due to the fact that we are removing a relevant and original characteristic from the tissue. That relevant and original characteristic is the donor cell. And the concern with those removal of donor cells are that the donor cells can be antigenic and can lead to calcification. So the removal of those are trying to remove a detrimental characteristic of the tissue, but unfortunately, that deemed these tissues to be more-than-minimal manipulation.

Finally, we have xenograft heart valves. These are heart valves derived from animal tissue, whether bovine or porcine, and they are regulated by FDA as a Class III medical device.

CryoValve SG Pulmonary Heart Valve is processed using our SynerGraft decellularization technology, which is designed to remove the donor cells and cellular debris. These valves have been implanted since 2000. There are less than 1,000 of them implanted annually. They are primarily used in pediatric patients and used at highly specialized centers. CryoValve SG is the only MMM allograft heart valve that FDA has cleared for marketing. It was cleared in three separate 510(k) submissions, and the CryoValve SG was found substantially equivalent to MM allograft heart valves.

Though MMM allograft heart valves are presently unclassified, they are currently 510(k) cleared and essentially regulated as a Class II medical device. The data we will present this morning has been previously reviewed by FDA with our 510(k) submissions.

This Advisory Panel is being asked to provide feedback to FDA as to the regulatory classification of AAA allograft heart valves, but to put this into perspective, it is important to note that tissue heart valves have been and continue to be regulated by FDA across a spectrum of different regulatory approaches. On one end, MM allograft heart tissues are regulated as human tissues, again, with general controls for manufacturing, good tissue practices, and without regulatory preauthorization. On the other extreme are xenograft heart valves.

The information we'll be presenting will show that MM and MMM allograft valves present the same kind of product risks and that both differ significantly in both the number and kind of risks that xenograft heart valves present. Given these differences, CryoLife believes that MMM allograft valves can and should be regulated in Class II. And, again, as a reminder from what Ms. Shulman said this morning, when Congress devised the classification, the goal was to put products in the least regulatory class.

We appreciate the opportunity to present our views, which support why we contend that MMM allograft valves should be classified as Class II medical devices. Our product has been safely implanted for over a decade in more than 4,500 patients. The safety of our product has been confirmed by our recently completed post-clearance study. The study design and endpoints were mutually agreed upon by CryoLife and FDA. And that study report will be available at the end of the year.

We are sharing with FDA and you, the Advisory Panel, our submitted comments in this presentation, the most up-to-date information from that study. Safety of our product has also been confirmed by an extensive review of our complaint files, medical device reporting, and the literature. There have been no changes in the product's safety profile, no publications identifying new or previously underappreciated concerns, and no anecdotal signals from research or clinical use of the product to suggest that they behave any differently than intended that would call into question the use of the 510(k) regulatory pathway.

The risks posed by MMM allograft heart valves are more similar to MM heart valves than to the more highly regulated xenograft heart valves. And, lastly, MMM allograft heart valves meet the definition of a Class II medical device, not Class III, because sufficient information does exist for consistent, reliable manufacturing, or using FDA's language, enough is known to establish special controls to ensure the safety and effectiveness of both CryoLife's product and future MMM allograft heart valves.

Like MMM allograft heart valves, Class II devices can be life sustaining or life supporting. The difference between Class II and Class III devices is not whether the devices are life sustaining or life supporting, as the FDA regulates over 200 cardiovascular using Class II special controls. But it's more important to note whether there is adequate information to establish special controls to ensure the safety and effectiveness of these products. Class II cardiac devices can play a critical role in sustaining and saving patients. Many, like aortic anastomotic clips used in bypass procedures, are permanently implanted medical devices. Some, like our CryoPatch SG intracardiac patch and LifeNet Health's

MatrACELL decellularized CardioGRAFT patch, are made from the same tissues and use the same or similar processes as our MMM allograft heart valve. The controls used for these products established their safe and effective use. Likewise, MMM allograft heart valves can also be safely regulated as a Class II device under similar controls.

The vast majority of methods used to process and test human tissues have a long history, are well-established, and have been used by FDA in clearing a wide array of medical devices. FDA has applied most of these methods to MM allograft heart valves through its various regulatory approaches with more than 50,000 MM allograft heart valves implanted over the past 30 years. These methods have been applied to MMM allograft heart valves over the past 10 years.

The decellularization method used by CryoLife has been reviewed and cleared by FDA for its effectiveness and application to allograft heart valves. FDA has pointed to examples of adverse impacts of decellularization on tissue integrity, calcification, degradation, and immunogenicity. However, these examples stem from publication where decellularization methods were used on xenograft tissues, not allograft tissues. Furthermore, these xenografts were exposed to ionizing irradiation for terminal sterilization of the tissue. For our MMM CryoValve SG, we have demonstrated using histology, immunohistochemistry, and residual DNA measurements a greater than 99% reduction in cells and DNA.

Additionally, the ability to adequately and consistently remove cells from allograft products through a variety of decellularization methods have a long, well-established history and have been used in a variety of human tissues, including dermis, bone,

periosteum, dura mater, and cardiac patches. The vast majority of these decellularized allografts are regulated by FDA as either human tissue or Class II medical devices.

Our processing steps remove the cells and cellular debris, as depicted in these histologic images. In addition, as we will show in subsequent slides, the antigenicity is reduced, valve recipient antibody responses occur at lower level and with much reduced frequency, and physical performance characteristics and structural protein content are unaltered by the decellularization process.

Interestingly, extensive clinical research has shown that MM allograft heart valves experience a loss of cells soon after implantation. This leads to a similar histologic appearance to the decellularized MMM allograft prior to implant. However, this in vivo cell loss comes at the expense of allosensitization to the recipient. The importance of the decellularization process is that it reduces antigenicity. Standard methods exist to measure the impact of the process, specifically, immunohistochemical assessment of residual major histocompatibility complex class I and class II antigens, and the assessment of reduction of panel reactive antibody, or PRA, after implantation. In the photos below, we show that residual alloantigen markers are reduced when cells are removed.

In addition to in vitro immunohistochemical staining, several clinical studies document a reduction in immune response in patients receiving our MMM CryoValve SG. As an example, in a published study by Hawkins and colleagues, a significant reduction in both class I and class II alloantibody measurements were shown for decellularized MMM allografts versus MM allografts. This is particularly important for pediatric patients with congenital heart defects, who may require future heart transplantation, as an elevation in

PRA correlates with a decreased number of possible donors for subsequent organ transplants and a longer time on the transplant waiting list. Moreover, the presence of preformed antibodies increases the risk for early solid organ failure and reduces patient survival after implant.

Importantly, decellularization does not adversely impact the material structure or protein content of the CryoValve SG valves. Well-published methods, including assessment of biomechanical properties, in vitro pulsatile flow, and fatigue testing, exists to assess these characteristics. CryoLife also used multi-photon laser scanning confocal microscopy to demonstrate that decellularization and cryopreservation of the CryoValve SG did not impact the structural proteins collagen and elastin. This technique, used in support of the clearance of our MMM CryoValve SG and CryoPatch SG medical devices, has been validated and is widely published.

FDA has indicated that MMM allograft heart valves present potentially unique concerns because no methods exist to assess recipient recellularization after implant. However, the published literature and our own assessment of explants demonstrate that no allograft, whether MM or MMM, exhibit significant recellularization with recipient cells, even after an extended period of implantation. Recellularization and subsequent tissue remodeling does not occur and is not required for the durability of the valve. As such, FDA is concerned with a lack of methods to assess a product claim that is not needed.

In the context of where these products fit on the risk and regulatory oversight spectra, the risks posed by MMM allograft heart valves are similar to MM allograft valves, which, as I mentioned, are not subject to premarket review and approval by FDA and that

the risks of these valves are significantly lower than those posed by Class III xenograft heart valves. In this slide, we summarize and compare the complaint rate data between our MM and MMM allograft products reported through our surveillance programs. To be fair, we also included the CryoValve SG complaint rates inclusive of events collected through active monitoring from clinical studies. The complaint rates for MM and MMM allograft heart valves are similar in both mean and annualized complaint rates regardless of the comparison.

Xenograft heart valves, on the contrary, present different risks due to their source material, degree of processing, and the potential for adverse effects that affect processing. They remain antigenic despite the processing. Their antigenicity can stimulate immune responses, and recipient responses can initiate chronic inflammation. And they must undergo potentially damaging sterilization processes while MM and MMM allograft products are aseptically processed.

The FDA has referenced literature describing risks of decellularized tissue, and as I stated earlier, these articles are specific to terminally sterilized xenograft products and are not relevant to the CryoValve SG or other MMM allograft heart valves. Importantly, these risks are not observed in the clinical data for the CryoValve SG. The specific reference to an increased risk of thrombogenicity has only been observed in studies of decellularized xenograft tissues, not allografts.

We have evaluated risks that are associated with all tissue heart valves, those common to both human and animal heart valves, those specific to human heart valves, those related to decellularization, and those related only to animal heart valves. The

observed risks for heart valves are the same both in type and frequency for MM and MMM allograft heart valves and differ significantly from the Class III xenografts. Therefore, further reasoning why MMM allograft heart valves support regulation as Class II devices.

Dr. Bill Northrup will now be presenting the post-clearance study results demonstrating the continued safety and effectiveness of the CryoValve SG. As you will hear, these clinical results support the classification of these devices as Class II.

DR. NORTHRUP: Good morning, Mr. Chairman and Panel members. My name is Dr. Bill Northrup, a board-certified cardiovascular surgeon during the 28 years I was in clinical practice in Minneapolis and St. Paul. I'm currently a Vice President of Physician Relations and Education at CryoLife, where I've been for the last 6½ years. And it's my privilege to present to you the CryoValve SG Pulmonary Human Heart Valve post-clearance study results.

As a reminder, the FDA set the standard for this study to include two categories of patients, which we've already discussed today, patients undergoing pulmonary autograft, referred to as Ross patients, and patients, a very heterogeneous population, as has also been recognized this morning, of typically young congenital heart disease patients undergoing RVOT reconstruction.

The FDA required a group of more than 120 patients over a span of over 800 patient-years of follow-up, with following metrics for safety, mortality, explant, re-operation, re-intervention, structural valve deterioration, which is defined essentially by hemodynamic parameters, which I'll discuss in a minute, and also calcification, defined primarily by echocardiography. Other metrics included endocarditis, thrombosis, thromboembolism,

nonstructural dysfunction -- of valve or leak, bleeding and hemolysis. In regards to function, echocardiographic assessment of valve gradients and insufficiency grades were also included in the study.

The conclusion of this study, as you will see, is that the 10-year outcomes demonstrate that the safety and function of the CryoValve SG is not different from MM allograft heart valves. No new safety signals were identified. No functional or performance concerns were identified.

The study set is fairly straightforward. There were 140 patients. I think it's important to notice that the mean age of these patients was only 20 years. Almost three-fourths of them were pediatric patients with an equal split between RVOT and Ross patients, with 802 patient-years of follow-up. In the retrospective group, as represented in the green on the left, you can see that the mean age of this very heterogeneous pediatric population is only 15.8 years. In the 60 prospective patient cohort, the mean age is higher because of a higher proportion of Ross patients relative to the RVOT population.

The 10-year safety data, and we have adequate data at this time point, show a 10-year freedom from mortality of 92%, freedom from explant of 93%, freedom from re-operation of 88%. Freedom from structural valve deterioration is 62% and may seem excessive, but keep in mind that this is an extremely young population, and we have known for decades that structural valve deterioration is accelerated in the young age with any kind of tissue valve, similarly with calcification. With regards to the other metrics, we can see the frequency of these is either nil or trivial at the 10-year mark.

With regard to freedom from structural valve deterioration for this very, very young

heterogeneous RVOT population, mean age of 12½ years, at 10 years freedom from SVD was 52%, compared to the older Ross population, where the freedom from SVD was 77%.

Similarly, with the freedom from explant data with these very young Ross patients or RVOT reconstruction patients, freedom from explant of 88% compared to 100% freedom in the older Ross patients.

If we look at the four valves that were explanted, they were all in the young age RVOT population, mean age of 9.4 years. They were explanted at a mean time post-implant of 9.2 years. Three were explanted due to valve dysfunction, and one was explanted due to suspected endocarditis in a patient with multiple valve replacements. All four pathology reports were received and nothing novo was reported. In fact, the findings were very similar to those of MM allografts, and pathology reports within literature reported risks, including intimal hyperplasia, varying degrees of cellularity, varying degrees of calcification, focal endothelialization, limited focal inflammatory infiltrate, and SVD.

If we look at the hemodynamic data in this post-clearance follow-up, we see the definition of SVD for the mean peak gradient equal to or greater than 40 mmHg. And we looked at the two cohorts in the retrospective group fall well short of this definition. Similarly, with the prospective group, both of the subcohorts also fell far short of the definition of significant gradient.

In regards to valve competency, if we look at these bar graphs, you'll see three colors. The green represents none or trivial, yellow is mild to moderate, and the definition of SVD is equal or greater than moderate to severe. In the retrospective RVOT cohort, we see 8.3% of the patients had SVD by this metric. In the Ross patients, it was 3.7%. And in

the prospective RVOT cohort, there were no patients with significant SVD by this metric. And in the Ross cohort, 5.1% of the patients had significant valve incompetence.

Finally, I'd like to just review some of the literature that I think supports concordance of several of the metrics of our post-clearance study. For review, we see that patient survival in the post-clearance study, 92% at 10 years, freedom from explant at 93%, gradients between 13 and 22, and occurrence of pulmonary insufficiency of a significant degree between 0 and 8.3% in this heterogeneous population. Some of these references you've already seen referred to today. You can see patient survival at various time points is similar, concordant with the patient survival in the post-clearance study, freedom from explant also concordant, gradients are concordant, and the degree of -- number of patients who had significant pulmonary sufficiency also concordant.

So, if we combine all of these patients, we have over 500 patients with CryoValve SG implanted with over 2,000 patient-years of follow-up. We have safety confirmed with low adverse event rates and efficacy confirmed through valve performance. Gradient is not increased, and the CryoValve SG remains competent, as indicated by regurgitant grades.

And, finally, published CryoValve SG also compares favorably with MM allograft heart valves, as reported in three case-matched institutional studies, the first from the University of Michigan reported in 2009, comparing CryoValve SG with a MM allograft in patients with a mean age of 5, follow-up approximately 5 years. We see a trend in favor of the CryoValve SG in regards to 5-year freedom from re-intervention and a significant advantage of the CryoValve SG in regards to 5-year freedom from significant pulmonary valve incompetence, and the mean peak gradients also showing a trend in favor of the

CryoValve SG over the MM allograft.

Second series is from the University of Utah, with 47 patients in each group, mean age of 9 to 10, with a 5½-year follow-up. Five-year freedom -- correction -- 8-year freedom from explant also shows a trend toward the advantage with the CryoValve SG over the MM allograft, and a 8-year freedom from re-intervention. Similarly, the mean peak gradient shows a trend in favor of the CryoValve SG, almost achieving statistical significance. And similar PI grades.

The final study, from the University of Illinois, shows a comparison of 39 CryoValve SG patients case-matched to 61 MM allografts. These were older patients, approaching age 20, follow-up beyond 5 years. The 5-year freedom from explant was clearly in favor of the CryoValve SG, and we achieved statistical significance in the 5-year freedom from global dysfunction -- or conduit dysfunction, with the advantage being to the CryoValve SG over the MM allograft.

So, in summary, we see concordance of clinical data in support of the CryoValve SG in regards to safety. There is a low occurrence of adverse events. There is a trend toward improved valve durability. And in regards to performance, we see satisfactory hemodynamic outcomes and a trend toward improved valve competence.

Thank you for the opportunity to present to this Panel.

MR. FRONK: All right. I know we are short on time, so I'll be very quick here with the last couple of slides. The centerpiece of Class II regulation is the effectiveness of special controls to provide reasonable assurance of the safety and effectiveness. CryoLife, in collaboration with FDA, in the review of our 510(k) submission, using this long list of

special controls, has shown by what Dr. Northrup presented a perfect example of how a Class II regulation is appropriate for more-than-minimally manipulated, or MMM, allograft heart valves.

With that, I would like to thank the Panel for the opportunity of presenting today. And myself and colleagues would be happy to address any questions that you may have.

DR. PAGE: Thank you very much, Mr. Frank [sic]. I really appreciate yours and Dr. Northrup's very clear presentation. Before I ask the Panel for any questions they might have for you, Dr. Northrup, I'm sure you overheard our discussion about -- just wondering per Dr. Ohman's question about the Bechtel paper, there were two Bechtel papers referred to on the FDA slides, one from '03 and one from '08. Your slide just showed the '08, which is a very short follow-up. By any chance, in your preparatory materials, do you have the mortality, which you showed very nicely as 0 for Bechtel '08? Do you know off hand the Bechtel '03? Otherwise, I think we're working on trying to find that report. If it's trouble, we can move on to the other questions.

DR. NORTHRUP: I'm going to ask Scott Capps, who has these references close at hand. I believe we can find it for you.

DR. PAGE: Okay. Unless it's immediately at hand, I want to go on to other questions from the Panel, and then you can let us know when you're ready to respond to that.

Dr. Zuckerman?

DR. ZUCKERMAN: Yes. Mr. Fronk, that was an extremely helpful presentation for this Panel today, but I would just like to ask you a clarification on one point. As you noted, a post-clearance study has been, I guess, completed by CryoLife. But just for the record, it's

my belief that the FDA has not seen the data that Dr. Northrup presented. And I would just like the Panel, as with other situations where the FDA has not independently reviewed the data, to take the data in that context. It's certainly very interesting data, and we look forward to also an external FDA review.

Thank you.

MR. FRONK: Thank you, Dr. Zuckerman. And I apologize. I think in my presentation I skipped the portion that we have promised to have this completed by the end of the year, and that would be the time you'd look at it.

DR. PAGE: Thank you.

Questions? Comments?

Dr. Hirshfeld and Dr. Lange?

DR. HIRSHFELD: Two questions about the statistical presentation of the data. You very nicely showed event rates for all the individual adverse outcome events, but you did not tabulate the complete event-free survival of the population, so we don't really have a feel for how many of these patients who received these devices actually were event-free at what time after receiving the device.

The second, which is related to that, is that you presented for hemodynamic performance mean values shown as bar graphs without any confidence intervals. But you didn't tell us what the fraction of patients were who exceeded the threshold values that you had defined.

MR. FRONK: Yeah. I'm going to let Scott Capps, our Vice President of Clinical Research, address that.

MR. CAPPS: I apologize. Could you please repeat the first question for me?

DR. HIRSHFELD: So the first question was very simple, that there's a long list of potential adverse events associated with the device. And your data presentation presented the frequencies for each one of those individual types of events, but did not show us a presentation in which we could judge what fraction of the patients actually truly had event-free survival over what period of time.

MR. CAPPS: Right. Okay. So, just to clarify, as we just heard from Dave Fronk, this is a very preliminary, very preliminary analysis. So we've just locked the database about 3 weeks ago in preparation for this meeting, so we've not really had a chance to look at that so far. But as we do analyze the data going forward for the final report, that's certainly something that we will work with FDA to report.

DR. PAGE: Thank you.

Dr. Lange?

DR. LANGE: I'm going to ask a question, and it's in the context of the adequacy of the special controls. The MAUDE database that the FDA presented, and I'll reference slide 36, with regard to pulmonary valves identifies structural problems in 18. More specifically, 10 of them occurred within 24 hours of opening the valve, 2 of them with thawing, and 8 of them within 24 hours of the valve being implanted. And it's represented that there were another five that within 6 months had structural problems. So that would be 2 to 3% of the valves, of the 500 valves. That'd be 10 to 15 of the 500 valves would have had structural problems either in the first 24 hours or the first 6 months. Do you guys have any insight as to what is going on with those valves? And, again, this goes to not -- I know we're not

evaluating the valve, but I'm trying to evaluate the adequacy of the special processes we have.

MR. FRONK: Yeah, that's a fair question. I think one of the things that we have to remember with all of these MMM or MM allograft heart valves is that they are cryopreserved tissues. They are stored at -196 centigrade. They are prone to cracking with mishandling. I believe Dr. Jonas brought it up this morning that there are a variety of factors that impact the handling of the tissue, and I think that attributes predominantly to the increased incidence that you see within -- what is elicited by the FDA's presentation is within the first day.

DR. LANGE: And would that be similar for the MM valve, a 2 to 3% structural issue?

MR. FRONK: Unfortunately, I couldn't give you a percentage of numbers, but what we find internally is that the outcomes are comparable in terms of propensity to have a handling issue, a crack or some form of deterioration due to the cryopreservation process regardless of processing methodology.

DR. PAGE: Thank you.

Dr. Cigarroa?

DR. CIGARROA: There was a slide presented with regards to the degree of insufficiency, mild, mild to moderate, moderate to severe. I didn't see the duration of follow-ups. It was hard for me to interpret that. The slide didn't have that on the legend. Could you bring that slide up and expand upon it, please? It was around slide 22 or 24.

DR. NORTHRUP: I think it's a little further. But this explains, first of all, as you can see, with the retrospective group, the mean follow-up period group is 8 years. And in the

prospective follow-up, the mean follow-up time is 2.7 years. So that's the context for that data. I think this is a little further along here. Next one. There we go. So what we have are valve competence, and we put these all together just with green as kind of go, none or trivial; mild to moderate is yellow; and the red is the red zone. That is the definition of SVD equal or greater than moderate to severe. And for simplicity's sake, we just stacked it. So here's your heterogeneous 12.5-year-old population with congenital heart disease showing 8%, roughly, of patients demonstrating significant insufficiency, as defined by this metric. The time period, again, for this group is 8-year follow-up. And the same for the prospective. The follow-up period is 2.7 years.

DR. CIGARROA: Thank you.

DR. PAGE: Thank you.

Dr. Kandzari?

DR. KANDZARI: This is a question for Mr. Fronk. And one of the concerns from FDA was temporal variability in processing or lack of standardization and processing. And one of the challenges of this deliberation is that we're representing a class, but we're talking about an *n* of 1 in terms of the devices. And at least with your particular technology, since 2008, has the processing changed in any way?

MR. FRONK: No, it has not.

DR. PAGE: Allow me to build on the question, Dr. Kandzari.

Your slide comments on the SynerGraft process, and there's a little trademark by it?

MR. FRONK: Correct.

DR. PAGE: Is that a proprietary process?

MR. FRONK: Yes, sir, it is.

DR. PAGE: So your specific process we're discussing is not available to another company who is developing an MMM device and performing a decellularization process?

MR. FRONK: Currently, no, and no company has approached us to do that. I think it's important to note that in the United States, right now, there are only two processors of allograft heart valves.

DR. PAGE: Okay. But --

MR. FRONK: Ourselves and LifeNet Health.

DR. PAGE: But in terms of my questions about the SynerGraft process, that is a proprietary process?

MR. FRONK: That is correct.

DR. PAGE: Okay. Thank you.

I have Dr. Slotwiner and then Dr. Lange.

DR. SLOTWINER: Thank you. That really was exactly my question. So, if another manufacturer wanted to decellularize, they would either have to create their own process or license yours; is that correct?

MR. FRONK: That is correct. And I think it's important for us to point out that what we're talking about is the controls that we went through in collaboration with FDA and we presented are the controls that would be used to evaluate that decellularization process, whether it is in the lab, in vitro testing, animal testing, and/or clinical. So I want to make sure that we're not fixated on the SynerGraft process but the fact that the controls do exist to evaluate those decellularization technologies.

DR. PAGE: Dr. Lange and then Dr. Furie?

DR. LANGE: So let me follow up on that on two hypothetical situations. One is, if your process changed at all, you were going to make a new and improved process to make these good results even better, would you want the FDA to approve that as a 510(k) or a PMA? In other words, would that new product be Class II or Class III? And if a new person enters the market with a decellularization process that's not exactly like yours but the cells still go away, would that be a Class II or a Class III?

MR. FRONK: Dr. Lange, our position is that they all should be considered Class II.

DR. PAGE: Actually, Dr. Doty had his hand up and then Dr. Furie.

Dr. Doty?

DR. DOTY: I have a question for Dr. Northrup. FDA has, in their presentation, brought concerns about possible increased infection due to non-sterile devices and also about potential risk of thromboembolism. Could you comment on the outcomes for the MMM devices versus standard allograft? And I think it's your slide 24 is the one that you have the data on the MMM devices. And maybe just sort of to give us a background on what those outcomes are for standard allografts.

DR. NORTHRUP: Yeah, John, let me go back and -- unfortunately, I was clicking all the way here because this is the way I typically give my talks rather than throwing all the data up at once. You're asking about --

DR. DOTY: Slide 24.

DR. NORTHRUP: Yeah, 24. This is 21.

DR. DOTY: So, in particular, your data shows that the freedom from endocarditis is

98% and thromboembolism is 100%. What is the comparison to standard allografts for those outcomes, as FDA has brought concerns about that?

DR. NORTHRUP: Yeah. I can't answer that question directly. Perhaps Scott Capps has more information? These are trivial numbers, first of all. And I believe that they're more or less the same for a MM, but I can't tell you that for sure.

MR. CAPPS: Yes. Scott Capps. Certainly, they would be comparable for -- given that this was the pulmonary valve. I think if you were to look at MM allografts on the left side, it might be different, but for the right side, they're very comparable in terms of freedom from endocarditis.

DR. PAGE: Dr. Furie, did you have a question or comment?

DR. FURIE: Yeah. It seems like as part of the 510(k), you've already accepted many of the special controls that were described as being consistent with Class III or PMA. What additional onerous responsibilities, I guess, beyond what you've already done would have to go into effect if it were to be a Class III device?

DR. PAGE: And, again, if you're not comfortable answering that, that really is a question that we would need FDA to weigh in on.

MR. FRONK: Yeah. I think from our perspective again, it all goes down to the lowest classification that's necessary for the product. And I think what we've shown is Class II is the appropriate, in compliance with what Congress planned with regards to these device classifications.

DR. PAGE: Well, I have one more question or comment, just clarifying. We will have another opportunity to ask questions at the very end of the open public comment, but go

ahead, Dr. Brindis?

DR. BRINDIS: Well, building on that last question, if we showed from the FDA slide 52, because I think it directly addresses the issue between a Class III with a PMA versus the 510 with special controls, and as I was listening to your presentation of the -- it seems like you have a lot of the special controls. That is -- can we show that slide, please?

MR. FRONK: We don't have FDA --

DR. BRINDIS: Can the FDA show that slide? Is that appropriate now, Chair?

DR. PAGE: Yes, I think it's fine to go ahead and -- because this is really at the heart of the matter, a full understanding by the Panel of the distinction among the different classifications.

DR. BRINDIS: Well, in the interest of time, as the slide is being put up, I mean, I was listening, and I heard the same thing that Dr. Furie heard, that there seems to be a substantial aspects of Class III already in place. That is -- and it needs to be further discussed -- there's premarket review of manufacturing, some sort of inspection, we're seeing an annual -- some sort of reporting process was presented to us, a review of significant manufacturing process changes was implied, and then of course, all of them have the appropriate bench testing and animal studies. The big difference in my mind -- again, maybe I need more clarification -- is the PMA requirement.

MR. PREBULA: My name is Randy Prebula. I'm outside regulatory counsel to CryoLife, and if I can answer just very briefly, many manufacturing processes for human-derived medical devices are, in fact, reviewed through 510(k) submissions -- sterilization, a manufacturing process that is typically reviewed through manufacturing process for

products that are sterilized. The difference between a 510(k) submission and a PMA, and I obviously defer to Dr. Zuckerman as the FDA representatives and others as well, but one of the key differences is that a manufacturing process change for a Class II device may be subject to further 510(k) review or it may not, depending on whether or not that manufacturing change could significantly affect the safety and effectiveness of the product. So there are controls in the 510(k) process that allow a company to decide whether a manufacturing change has altered the product in a way that requires a new 510(k). They don't require PMAs when you simply modify the manufacturing process. I hope that helps clarify.

DR. PAGE: That's a very helpful clarification, sir. But if I'm clear on what you just said, the decision is made by the manufacturer as to whether it's -- it merits further review?

MR. PREBULA: It is subject to the company's determination and FDA review through either inspection or further follow-up, yes.

DR. PAGE: But if the company decides it's not subject to review, does it ever go to the FDA?

MR. PREBULA: Yeah. It can go to FDA. It frequently goes to FDA --

DR. PAGE: But is it required to go to the FDA?

MR. PREBULA: It is not required to go to FDA.

DR. PAGE: Okay. That's an important distinction for the Panel to understand, that the changes in manufacturing are self-reported as opposed to obligatory in being reported in a PMA device.

We are pulling up a slide, I believe?

In the meantime, I saw someone with a manuscript over there that -- did you happen to find that Bechtel 2003 or has FDA identified the -- just we're looking for the mortality just out of interest for that larger study.

MR. FRONK: And while he quickly pulls that out, Dr. Lange, I want to point one clarification to your question about the early structural issues on that. We need to make sure that we're referencing the appropriate timeframe. That was over a 10-year span and almost 5,000 implants, not 500 that you referred to. So the data you're referring to is almost an order of magnitude off in terms of frequency of percentage.

DR. LANGE: Okay. I'm sorry. I thought one of your slides said that you had over 500 implants with 2,000 patient-years.

MR. FRONK: That was the data from published clinical studies.

DR. LANGE: Okay.

MR. FRONK: The overall experience that CryoLife has had with that is approximately 5,000.

DR. LANGE: Great. That's very helpful. Thank you.

DR. PAGE: We may well have questions for the CryoLife people again as we deliberate. I really appreciate it. Very nice presentation.

Dr. Zuckerman?

MR. FRONK: Thank you, Dr. Page.

DR. ZUCKERMAN: Okay. So, you know, as Dr. Brindis indicated, this is a key slide, because certainly, from the FDA perspective, it shows us with the PMA process, we already have all the necessary bells and whistles that are appropriate for regulation of a challenging

device like more-than-minimally manipulated heart valves. While there are possibilities through the Class II process to approximate what can be done with the PMA process, it's important to recognize that Congress specifically made the Class III process for a purpose.

And, for example, let's go back to Dr. Lange's astute question. For the so-called 510(k) process with certain changes, they wouldn't necessarily be required to be reported to FDA, as opposed to our regulatory authority with PMAs. Or you just heard about, with respect to the manufacturing process, an inspection, yes, there are some abilities under Class II. But, you know, there, we need to be more careful, more parsed out, and we already have a process under Class III. The same thing with an extremely important post-clearance study that you just heard about and we should be seeing in the near future. Look at the difference between standard FDA regulatory authority in the PMA process versus, again, some of the increased difficulties that are encountered when we go through the Class II regulatory process.

So I think the net sum of this is that Dr. Nell has tried to indicate that we already have a process that is designed for this type of challenging situation to handle all perturbations that might be encountered for an important class of devices.

Dr. Nell, do you want to add anything?

DR. NELL: Thank you. Actually, I would like to just give just an example of what could happen if these were Class II devices. I'm going to separate from this slide for just a moment. So we see in this first example Simon report in 2003, these were decellularized porcine heart valves. Now, porcine heart valves are regulated as Class III PMA devices. They are sterilized bioprosthetic valves. But let's take, for instance, if they were Class II

devices, and if this device had been on the market as a Class II device, the manufacturer could have decellularized this product without coming into the FDA and just began marketing it, because it's up to their -- it's their purview for this type of manufacturing change to submit to the FDA. So in this case, they would say, okay, we've decellularized it, we've looked at it, we don't see any significant differences, so let's just go ahead and start marketing it. And we see in this case that we had three patients die within a year. I don't think we really want to see that happening given the variability that can exist in decellularization techniques and methods, the fact that there aren't any standards out there to dictate how the companies are going to actually be decellularizing and be evaluating their products after they're decellularized.

DR. PAGE: Thank you.

I want to be mindful of the time. I also want to be mindful of giving the representatives from CryoLife the best opportunity to present their perspective. And I'll remind the Panel that unlike when we're working through an approval process and when we have a sponsor -- I see your hand, sir -- when we have a approval process, we do give the company, the sponsor, the last word. There is no sponsor here. That being said, I do really want to make sure we're giving a fair voice to the CryoLife representatives. So I will ask you to give a summary statement. We may ask for other questions or clarification during our deliberations. But I do want to provide you as close to the final word as possible before we proceed with the rest of the open public comment section.

MR. PREBULA: Thank you, Mr. Chairman. Just very briefly, on behalf of CryoLife, as their outside regulatory counsel, again, my name is Randy Prebula, the company feels that

the special controls that have been developed for this product are adequate and appropriate. It's important to note that any manufacturer of any MMM allograft product that were to modify their manufacturing process and fail to validate the impact of that process on their product and do a regulatory assessment would be violating FDA regulations under the good tissue practices and good manufacturing practices and QSR requirements. So while Dr. Nell is correct that there is a risk that changes could impact a product, they are required under special controls and general controls for Class II devices to be adequately validated before they're marketed. Thank you.

DR. PAGE: And, again, just so I'm clear, that adequate validation is interpreted by the company, and any decision to report to the FDA that results is completely the company's choice?

MR. PREBULA: That is correct, subject to review --

DR. PAGE: Okay.

MR. PREBULA: -- inspection.

DR. PAGE: And that's what we're wrestling with here, sir.

MR. PREBULA: I understand that. I just want to make sure it is clear that they would be violating FDA regulations without having done such validation.

DR. PAGE: They'd be violating regulations if they didn't evaluate it, but they would be violating no regulations if they interpreted the data however they're going to --

MR. PREBULA: Correct.

DR. PAGE: -- interpret them and then failed to report those data and the changes to the FDA?

MR. PREBULA: That is correct.

DR. PAGE: Okay. We're all in agreement there. And does the Panel understand?

I would like to now proceed with the General Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel to present data, information, or views relevant to the meeting agenda. You've already heard Ms. Waterhouse describe the process for Open Public Hearing, and we're still in that. So we don't need to hear it again, much as we enjoy hearing it each time.

(Laughter.)

DR. PAGE: There are four requests to speak. Each speaker will be given 5 minutes to address the Panel, with 1-minute warnings. So, at 4 minutes, you're going to get the yellow light. Once you have been asked to approach the podium, please be sure to state your name, company, and any affiliation you may have with the entities presenting today. And I really ask the presenters to maintain the 5 minutes. So, if your most important statement is at the end, I hate to cut you off, but I have to, in fairness to the process.

The first speaker is John Brown from Indiana University School of Medicine. Welcome.

DR. BROWN: Mr. Chairman, Panel members, FDA staff, thank you for the opportunity to comment on the MMM allograft heart valve classification. I'm John Brown, and I'm the Harris B. Shumacker Professor Emeritus of Surgery at Indiana University School of Medicine, and I've had a background of nearly 40 years in dealing with RV outflow tract reconstruction. And I've used virtually all of the pulmonary valve substitutes that have been tried over the last 35 to 40 years.

Pulmonary valve replacement in children is the most common valve to be replaced or to be required to be replaced. It's four times more common to replace the pulmonary valve in children than is the aortic valve. So this pulmonary valve is a very important product in my treatment of congenital heart disease. We put over 1,000 pulmonary valves in children, my two colleagues and I, over the past 30 years.

I should say my travel to this meeting, to attend this meeting was paid for by CryoLife.

My comments are twofold. I wish to share my clinical experience with the MMM SynerGraft CryoLife valve at our center and to comment on how it has been used in my practice of congenital heart surgery.

We've used over 100 implants since 2002. We were one of the early adopters when we saw that there were some midterm degenerative processes with the standard valve, and we adopted early the SG process. The handling characteristics, in my opinion, are no different than the standard processed allograft valves. And the outcomes have been quite competitive with other right ventricular outflow tract reconstruction options.

I participated or our center participated in the 510(k) study that was -- and I was the lead author of the peer-reviewed publication, and we've also participated in the post-clearance study.

This is, I'm sorry, a little difficult to read, but basically, what it shows is that the SG valve has less obstruction at the 4-year follow-up in this multicenter study and has significantly improved lack of regurgitation at 4 years in this follow-up study.

And I'm going to skip to the next slide, in the interest of time. I think this graphically

demonstrates that, really, both the MM and the MMM valve in Ross patients actually function quite well, with a graft on the left side, looking from freedom from explantation. If we look in the right ventricular outflow tract group of patients, there is a trend towards improved outcomes in patients who received the SG processed pulmonary valve.

This slide demonstrates the degree of regurgitation, which I think is one of the more important features of the SG valve. My patients -- this valve functions more like a valve for a much longer period of time than the standard processed valve, as you compare Ross patients in the two left columns with the standard RV outflow tract columns in the right side. And the degree of none, trivial, or mild regurgitation makes up nearly 80% of the patient population.

I use the SG valve primarily in patients undergoing the Ross aortic valve replacement, which is very popular at our institution, and I've been doing that operation at our institution for more than 20 years. 95% of the allograft valves that we put in the pulmonary position are still in the pulmonary position, indicating that it's been a very durable process, and our studies would indicate that the SG process should lengthen that even further.

This is graphically shown in this diagram, showing that at least there is a trend that the SG process enhances the durability of the valve.

I guess, in summary, I am hoping this proposed classification change doesn't take away from my patients what I consider to be a marked improvement in our ability to treat children with congenital heart disease. If this takes us off the market, we're going to be going backwards instead of forward. I think there is substantial evidence that the SG

process has improved the outcomes in my patients.

Thank you.

DR. PAGE: Thank you very much, Dr. Brown.

Our next speaker is Dr. Richard Ohye, University of Michigan, Mott Children's Hospital, Congenital Heart Center. I know I probably mispronounced the name. Oh, there we go.

DR. OHYE: I'd like to thank the Committee for allowing me to come and give public testimony today. I'd also like to thank the Committee for allowing me to do this by video, as I ruptured my Achilles tendon last week and just had it repaired.

My name is Richard Ohye. I am the head of pediatric and cardiovascular surgery at the University of Michigan in Ann Arbor, Michigan. Our center is one of the largest in the country. We do about 900 or 1,000 cases a year of which about 5 or 6 hundred are open. We use a lot of cryopreserved allografts, probably one of the largest users in the country. As far as the SG technology, I've probably put in about 125 or so, and we've probably put over 200 in as a program, so I feel very comfortable giving testimony about how this technology is important for my patient population.

You know, I think, in general, I wasn't going to give too much background on the technology or about the regulatory aspects. I mean, that's not my bailiwick. It's more for the company and for this Panel.

But, you know, I think about this in terms of removing a detrimental product of the allograft rather than adding something new, not unlike if you treat with antibiotics to remove bacteria or washing it to remove a clot or particles, fat lobules, white cells. And it's

removing something that's detrimental, in this case, removing cellular debris. And that really is sort of the background of why it's very helpful for my patient population, because it's this cellular debris that remains within the allograft without the treatment technology that incites an inflammatory or an immune response.

And that causes two things. One, we've found that when we look at about 160 or so of the SG grafts and compared it to about 125 aged-matched and diagnosis-matched controls from three different centers, we found that the SG-treated grafts lasted longer in terms of they weren't as leaky over time, and they didn't become as narrowed over time. And that's important in our patient population, because our kids will need their valves replaced repeatedly over time. And if you can save a child an operation over their lifetime, it's a very important -- the difference between having three operations versus four operations is a big deal for a kid.

The other thing that's very important is that a percentage of our patients will ultimately come to need heart transplants. We're not always successful in repairing these things in a permanent, durable way. And now there's estimated to be about a 1.3, 1.4 million survivors of congenital heart disease that are adults, and many of these will require a transplant.

The other thing that happens without the SG technology is that the cellular debris that's left behind causes an immune reaction, which is persistent. And so what we do is when someone comes to heart transplant, we measure what's called a PRA, or a panel reactive antibody. And what it is, is it tells us what percentage of people in the general population a person will react to. So, if you think about a person waiting for a heart

transplant and someone goes to donate, and it's only a small fraction of the people that donate in the world, and if your PRA is 50%, that means you react to 50% of those people. So that small fraction, only half of them you'd be eligible to donate -- or to receive a heart from. Some of my kids that have received regular allografts have PRAs of 99%. And that means out of that small fraction of people that donate, only 1% would be eligible to give a heart to that child. And so finding that needle in the haystack is, frankly, not going to happen. And those types of kids usually die on the wait list waiting.

So, with the SynerGraft technology, we're able to decrease that immune response. And in the kids that have gotten SG grafts that we've seen going forward, their PRA is very, very low, and it's not been an issue to get transplants. So, from my standpoint, this is really an important technology. It improves the longevity of the grafts, which equates to few operations for my patients. It also decreases their PRA, which improves their chances of getting heart transplants in the future.

So, again, I'd like to thank the Committee for the opportunity to give my testimony. If you'd like a reprint of the article that I referenced, it will be available at the meeting, or if you'd like to ask me any questions, I'll be available by cell phone from home.

Thank you.

DR. PAGE: Okay. Kept within time.

(Laughter.)

DR. PAGE: Our next speaker is Alyce Jones. Dr. Jones is representing LifeNet Health.

DR. JONES: Good morning. I'd like to thank the Chairman and the Panel for the privileged of presenting this morning on LifeNet Health's position on the regulation of

more-than-minimally manipulated allograft heart valves. LifeNet Health, just to acquaint you, we are the other processor in the United States of allograft heart valves. We have over 30 years of experience and have distributed over 40,000 lifesaving cardiac and vascular allografts. Germane to this conversation this morning, we have distributed over 1,100 more-than-minimally manipulated cardiac patches for RVOT repair. I'd like to note that all of those have been without incidence or report in the MAUDE database. We also have the longest running accreditation by the American Association of Tissue Banks and have been ISO certified for quite some time.

We have been working with our collaborators, Dr. Richard Hopkins and Dr. Steven Hilbert, and have over 10 publications in the peer-reviewed literature, two of which are clinical and were not included in the FDA's review of the relevant literature this morning. Also, we have been relying on FDA's guidance over the last several years in the development of our own MMM allograft heart valve. The direction has been 510(k) with a clinical trial.

Therefore, our position is we feel that it's appropriate to continue to regulate MMM allografts as a Class II device. The CryoLife team this morning very elegantly pointed out all the special controls that are currently in place and that we also utilize to ensure the safety and effectiveness of these allografts and the safety of the American population.

The concerns are, in part, regulated -- are satisfactorily addressed by the existing general controls. One thing we would suggest is if FDA feels that there is a lack of special controls or science out there, that there would be an FDA and industry partnership to develop the special controls and publish them. We would also like aortic and pulmonary

valves that are decellularized to be considered separately.

The benefits of allograft heart valves have been well described this morning, and generally, their failure mode is not catastrophic, especially in the pulmonary position. Because they are allograft and human in nature, they maintain the correct hemodynamics and low-transvalvular gradients. There's minimal potential for thromboembolic events, no lifelong anticoagulation, natural pliability and compliance, and they're less prone to infection and lower biocompatibility concerns. And they do not require lifelong immunosuppressive therapy.

One of the things of note is, again, in the FDA literature, they were talking about decellularization of porcine tissues, bovine ureters. And, again, that is not the subject of this discussion. It's allograft heart valves.

FDA has raised four major concerns we'd like to address. The infection and allosensitization are also associated with the Class II MMM patches and the 361 valves that go through no sort of regulatory premarket approval. Lack of prospective randomized trials. There are objective performance criterias out there, and there is a well-known natural history for the failure mode of the cryopreserved allografts. And there are also perceived ethical issues with randomization in the pediatric population. Again, FDA feels that there is a lack of established methods, and we would say that ISO 5840 is an excellent backbone, providing many special controls, in addition to others in the literature. Lack of manufacturing and inspection controls. FDA has authorization for inspections and postmarketing surveillance. The current controls under 510(k), again, the backbone being ISO 5840 and robust preclinical bench and animal data, human clinical studies, and a

guidance for industry written by FDA on the animal studies. Design controls are at the heart of what we do to ensure safe and effective graft, manufacturing site inspections as well as postmarketing surveillance.

Some of the risk mitigation strategies that we feel are available are applicable to the heart valves and to the pulmonary allograft patches that are already out on the market as a Class II device. From a life sustaining, the animal model detailed in 5840 and the human clinical trials meet that need. Disease transmission is very well addressed in 21 C.F.R. 1271 and good tissue practices. The sterility testing performed on these valves is the same as for parenteral drugs, IV drugs that you give in your practices every day. Immunological response, again, can be addressed via 5840; MHC I and II immunohistochemistry in the clinical trials; calcification and degeneration, again, 5840 via the animals and the clinical trials.

So under- and over-decellularization are potential failure modes. These are the tests that we would suggest in the special controls and also that CryoLife had on their slides as well.

Again, FDA's concerns with manufacturing. There's detailed manufacturing information in the IDE, 510(k)s they can inspect, and there's a desire to conduct preapproval manufacturing inspections. Again, Section 704 gives them this. The one big difference between the two processes is the fee involved is a quarter million dollar submission for it, with ongoing maintenance fees.

And, in conclusion, we feel it's appropriate for FDA to continue to regulate --

DR. PAGE: I thank you very much.

Our final speaker is Christina Silcox, Senior Fellow at the National Center for Health Research. Welcome.

DR. SILCOX: Thank you for the opportunity to speak today. I'm Dr. Christina Silcox. I have a Ph.D. in medical engineering and medical physics from MIT and Harvard Medical School, and I am a Senior Fellow at the National Center for Health Research. Our research center scrutinizes scientific and medical data and provides objective information to patients, providers, and policy makers. These are the perspectives I bring here today. We do not accept funding from pharmaceutical or device companies, and so I have no conflicts of interest.

We support the FDA's recommendation that more-than-minimally manipulated (MMM) allograft heart valves be classified as Class III devices and therefore subject to the premarket approval process. All other types of heart valves under the oversight of the Center for Devices and Radiological Health at the FDA are classified as Class III. There is no reason that these heart valves should be an exception.

MMM allograft heart valves are indisputably used to support and sustain human life and are of substantial importance in preventing impairment of human health, which is the definition of a Class III device.

Only Class III devices are subject to premarket manufacturing process review. Manufacturing processes are critical to the safety of this device. In addition, the effectiveness of MMM heart valve are also highly dependent on the manufacturing process, affecting the performance and longevity of the valve and the likelihood of immune rejection. There is currently insufficient information to determine all the general and special controls that would be necessary to provide reasonable assurance of the safety and effectiveness of this device in order

to classify it as Class II.

Certainly, clinical trials would be one type of control needed. Currently, most of the information about these devices consists of small studies, under 50 subjects per valve type, often funded by a single device company. None of the studies were randomized and only half included a control group. That's the -- information we saw today that hasn't been published yet.

Few studies looked at the immunologic responses of the MMM valves, and only two of those did a comparison of MMM valves versus standard allograft valves. Follow-up of all four immunological studies were 1 year or less, which is not enough to tell us how safe or effective these valves were. Most studies of MMM heart valves have focused only on the resulting heart valve function. As a result, we have almost no information about other potential side effects. Postmarket study data from the single currently approved MMM allograft heart valve is not currently available, and when it is completed, it will focus on pulmonary valve replacement, which studies suggest is much less immunogenic than aortic valve replacement.

To summarize, heart valves are high-risk devices, and that's why all other heart valves regulated by the Center for Devices are Class III. Given MMM valves are relatively new, with limited information available about exactly how the processing changes the tissue over time, we do not know enough to control potential risks with special controls. For example, mechanical valves have been used in humans for over 50 years but are still in Class III because a 510(k) with special controls are not considered sufficient to protect patients' lives.

We recommend the Advisory Panel vote to classify these devices as Class III, which will save lives by ensuring the safety and effectiveness of these devices be proven in well-designed clinical trials and premarket inspections.

Thank you very much.

DR. PAGE: Thank you very much.

Does the Panel have any questions for the Open Public Hearing Speakers?

(No response.)

DR. PAGE: Seeing none, I now pronounce this portion of the Open Public Hearing to be officially closed. We'll proceed with today's agenda.

It's now time for Panel deliberations. Although this portion is open to public observers, public attendees may not participate except at the specific request of the Panel Chair. In addition, we request that all persons who are asked to speak identify themselves each time. This helps the transcriptionist identify the speakers.

Now, we had one bit of homework for the FDA about that one paper. Did we ever get the answer from either the FDA or our other colleagues?

Yes, sir?

MR. CAPPS: Can I clarify which paper specifically you wanted?

DR. PAGE: It began with a B. It was a 2003 large series.

MR. CAPPS: There was a smaller series in 2003. There were no mortalities in that publication if it's the Bechtel.

DR. PAGE: Can someone remind me of which slide FDA put up that listed data and as was pointed out by Dr. Ohman?

Yes, Dr. Ohman?

DR. OHMAN: It was page 23, I believe, at the bottom right-hand corner. It's the largest series published, and I was interested in it because it actually is an order of magnitude larger

than any of the -- well, most of the other studies. Therefore, I think there was a study by Dr. Brown, and he presented as well --

DR. PAGE: Yes. Your presentation included the Bechtel follow-up for a 2008 paper that included 66, but I was just asking -- I don't want to get stuck on this issue because it's relatively minor to the issue at hand, but there was as Bechtel 2003, and slide 24 makes note of a sample size of 342. We were just looking for the mortality of that study. You showed the mortality for the very short follow-up Bechtel. I thought you might have had the older one available.

DR. OHMAN: Can I clarify? That's a study by --

DR. PAGE: And I'm sorry --

DR. OHMAN: -- and Dr. Brown presented that date in the public hearing.

DR. PAGE: Oh, you're right. That is Dr. Brown's, not -- there are two columns here. So we have the data for that larger study?

MR. CAPPS: We do.

DR. PAGE: In terms of mortality?

DR. OHMAN: Great. Thank you.

DR. PAGE: Okay. Fine. And the mortality was?

DR. JIANG: This is Helen Jiang from FDA. So the Bechtel paper you referred to, they didn't talk about mortality, just to clarify. Three of those papers we used from 2003, '5, and 2008, none of them talk about mortality. But the Brown 2010 is the largest sample size, which is a national registry. They involved seven centers, SG use device. And so the mortality, there are four of those are possibly -- let me see -- where was the set -- four of them are possible valve related. Okay. Let me get the exact wording.

DR. PAGE: The reason Dr. Ohman asked was there was a very broad spectrum in terms of mortality, and the answer that we're hearing is in the large study, the mortality was relatively low. Does that satisfy your question, Dr. Ohman? Perfect.

DR. JIANG: For the --

DR. PAGE: Great. So now we're going to go on with the -- with our own deliberation. I do want to acknowledge our Consumer, our Patient, and our Industry Representatives. I will ask you for comment at the end of the session. Does anybody have any questions or comments at this time?

(No response.)

DR. PAGE: I'm seeing none. Great. Thank you.

And now I'll open the discussion to the Panel in terms -- before we start undertaking the specific questions, I'm interested in comments, concerns, questions about where we are in this process. Again, we've talked a lot about one company's valve. We're talking about a class of devices in terms of how they will be regulated going forward. And while I was struck by the comments from the two surgeons who spoke about using this valve, we need to be mindful that we are not looking to take away established technology, but our job here is to give the FDA guidance in terms of regulation of this class.

I see Dr. Cigarroa and Dr. Brindis.

DR. CIGARROA: So I certainly am impressed by the data presented by the one company. I, too, however, want to make sure that we as a Panel don't take a look at the various datasets and lose sight of the issue of the distinctions in controls between PMA Class III and Class II. And I think that really is the issue here, as you have stated, Dr. Page.

DR. PAGE: Thank you.

Dr. Brindis?

DR. BRINDIS: Yeah. To build on that point, I think it's really important that we try to stay at the 30,000-foot view related to this question. In fact, a number of years ago, the FDA commissioned the Institute of Medicine to comment on the 510(k) process as to does this assure safety and efficacy, particularly related to a lot of medical devices. And we can discuss the IOM report, and I'm sure it's debated even within the FDA itself related to the IOM recommendations. But they basically had a lot of concern about the 510(k) process particularly related to predicate devices, in terms of their safety and efficacy. So one could look at that this as really answering some of those queries. If you have a new product in this arena, the MMM arena, you know, how are we going to assure that this predicate device has the same safety and efficacy. And I think that my interpretation of CDRH bringing forward this issue to the Panel is, in many respects, reflects some of the concerns raised by the IOM report.

DR. PAGE: Thank you, Dr. Brindis.

Dr. Somberg?

DR. PAGE: Well, I -- you brought up the Institute of Medicine report because there were many flaws in it. And I think a correct summary would be the FDA did reject the Institute of Medicine report. So, with that said, I'm -- also like to look at a 30,000-foot view. And there are distinct differences from a 510(k) and a PMA. And I certainly have served, I think it's 10 years now, on this panel. And with that, I would -- from the very beginning was always in favor of clinical studies. But I must say, I was very impressed today, and prior to that even, by reviewing the industry submission that came about a week ago, that in this area, it seems to me the 510(k)

approach has worked. We have one company that has fulfilled its initial work by following the special controls that were listed and had a clinical study with the 510(k), which is possible, and then had a follow-up study and is coming to fruition here. That's more than many PMA companies do in terms of their requisite report, a postmarketing study.

And then we see another -- there are really only two players in this area, and we see -- what's it -- LifeNet -- I got the intimation that they're thinking about it. They have guidances. They've discussed it with FDA. There are controls, and they are going to follow this pathway, too. So I'm unsure of why, with all the problems in the world, and even reducing that to the regulatory world, why we are focused in this area, where I don't see a major problem and many areas I have seen major problems. So I'm very loath to change what is working.

DR. PAGE: Thank you.

Dr. Doty?

DR. DOTY: So John Doty. So I want to comment. I agree with you. I don't think we need to change what's working. I wanted to comment on what Dr. Brindis said. And I share your concern about how do we assure in the future that a new process doesn't come in. I think the difference is we don't have a predicate device here. We've got a predicate human valve, and now we've got a process, and that changes that human valve now to a device, which I think is an artificial construct, and it leaves us with a very unique product that we use. And so I would favor what Dr. Somberg says. Why change what's already worked, the scientific literature supports, and has been performed according to what the FDA has required in the past.

DR. PAGE: Thank you.

Dr. Kandzari?

DR. KANDZARI: Just also want to level-set this conversation with a response from Dr. Zuckerman, because in other classification panel meetings, we -- this is not a unique situation where there may be one, two, or a very limited number of device technologies commercially available for a broader category or class of what now may evolve into what we consider a device. And, in certain instances, as has been previously mentioned, special controls may have already existed. They may have been fulfilled already by a selected manufacturer or manufacturers. And our impression oftentimes, as it is for sponsors or manufacturers, is that if they are categorized as Class III, they're going to have to now perform a broader randomized clinical trial. But that's not the case, is it? Because there are instances in which existing data may already exist within, and the company can use that to still support the PMA classification. Is that correct?

DR. ZUCKERMAN: Yes. Well, let's take a step back. What is your fundamental question or concern? The burden of the clinical trial, Dr. Kandzari?

DR. KANDZARI: Yes. And that in selected instances, a manufacturer may already have existing data that would help support the PMA without additional burden?

DR. ZUCKERMAN: Right. I do want to underline that point, that for a Class III device, the requirement is a reasonable assurance of safety and effectiveness, and one size doesn't fit all. And certainly the FDA has clearly recognized that for a device class like this, a randomized clinical trial of 5,000 patients is not needed because it's not doable. And you've seen that there are other pathways, as evidenced by the nice data that the CryoLife people have shown this morning. But it's really important to understand that we're talking about a general approach to a device class, an appropriate regulation. An appropriate regulation involves more than the

clinical trial, even though we're all clinicians and we focus in on that. It involves proper and appropriate assessment of preclinical data.

And while fortunately we've had success in this field, the sample size, as everyone is pointing out, is extremely limited, an *n* of 1 cleared product. The science is still developing. And while there is an ability to understand some processes, there are multiple question marks, A; B, I think in addition to the discussion of the 510(k) report and pluses and minuses of the whole process, it's important to recognize, especially in the heart valve field, we have had our successes and our non-successes frankly.

DR. PAGE: Thank you.

I saw Dr. Ohman raising his hand, but I do want to just help frame the discussion. And the FDA can correct me if I'm wrong here, but no matter what this Panel recommends, these devices aren't coming off the shelf tomorrow or the next day or the next day. To the contrary. I think there are compelling data that this device we've talked about today has a role and advantage, and the last thing I would do is sit here and allow a process to go on that would consider eliminating this from being available to very often the young people who need it.

That being said, we are here to discuss the class of device. So the fact that we are comfortable with one device in this class is one thing. We need to consider what happens with reclassification, or I should say, classification to Class II. And as we heard acknowledged, the level of regulatory oversight is less. It is voluntary. If they change plant, if they change process, the manufacturer, this manufacturer or another, is under no obligation to report that to the FDA as a Class II. Only under PMA is there obligation. So we're going to voluntary reporting versus not. That's just one example of the difference in terms of the regulatory process. We're here to

discuss the regulation of this class of device, but I'm taking it as a given, with the assurance from Dr. Zuckerman and the FDA, we're not talking about this device coming off the shelf. Actually, the least burdensome process to allow a PMA is what the FDA is committed to in terms of moving forward to find a way that this specific device we're talking about could potentially be available in a continued way.

Am I accurately reflecting your response to my concerns earlier, Dr. Zuckerman?

DR. ZUCKERMAN: You're doing an excellent job. And to provide a little bit more granularity, following this Panel meeting, the FDA would take some time to review the Panel transcript and then publish a proposed rule in the *Federal Register*. Then there is a period of time for comment in the *Federal Register*. The Agency then has to carefully review all the comment and come out with a final rule. And if the final rule was a classification for Class III, the Agency would have a stipulation that manufacturers would have about 30 months to submit a PMA. In addition to that, there is regulatory discretion. So the key point is that no final decision is occurring before Christmas, A; and B, that this is recognized as an extremely serious matter, because we're dealing with very important life-saving devices, and our intent, regardless of final decision, is to make sure that you as physicians have appropriate access to this technology.

DR. PAGE: Thank you, Dr. Zuckerman.

Dr. Ohman and then Dr. Slotwiner?

DR. OHMAN: So this has been a most interesting morning, I must say. I have really enjoyed hearing the arguments for and against Class III and II. I have to say, as I look at the information and as I look at the environment, it's hard to say that we have a valve who has some post-explantation processing that we can talk about in the future, that we don't know

what it might be in the future, that we would simply say, that's okay, that's a Class II, where all other valves that are artificially implanted are all Class III. So it's obviously a very important part. And so, to me, the discussion is, yes, we need these, the regular pathway should not be burdensome, but it is a very important area. And what we're talking about today is really more the future than what's existing on the table. And I think that's a very important part.

So bear with me for a second. My Irishness may be coming out. But let's, for argument's sake, say that we had a new way of doing heart transplantation, and we actually decellularized some of the hearts, and we had a new process to that. Would we say that that's still a transplant in the old-fashioned way, with no regulatory issues? Or would we say this really ought to be a Class III because there is a whole host new way of doing it. And I think, okay, we're just talking about the pulmonic valve, but the heart and this bigger issue is really what we're talking about.

And so, to me, it would be awfully hard to say every other valve except this one is going to go down this path, because I really do believe that it's hard for us to predict the future. Everybody has a cell phone here. Had we had this panel 15 years ago, nobody had been looking down in their areas to see what's on the phone. So it's a very hard thing, to look forward. But I think in this scenario where these are children, by and large, who have very difficult issues, to me, it would be awfully hard to make that a simple, to some extent self-regulated but not completely, process. To me, it really is more in the Class III arena.

DR. PAGE: Thank you, Dr. Ohman.

Dr. Slotwiner and then Dr. Yuh?

DR. SLOTWINER: Thank you. And this is a question building upon Dr. Ohman's

statement. We're talking about this class of more-than-minimally manipulated allograft heart valves and one particular process, decellularization. But is it possible that a totally separate tissue processing could be considered under this MMM allograft and then be regulated under Class II, or would this specifically be a decellularization process? In other words, if we vote for Class II, would we be opening up an opportunity for an unforeseen type of tissue processing that perhaps none of us have imagined?

DR. PAGE: Is that a rhetorical question or a question for Dr. Zuckerman?

DR. SLOTWINER: No, it's actually a real question for Dr. Zuckerman.

DR. ZUCKERMAN: Okay. Dr. Nell may want to comment also. But if we go to FDA slide 6, I think there is an opportunity, as you say, for under the MMM category for new processes that we really haven't thought about right now, given the generalized nature of how we're defining MMM.

Dr. Nell?

DR. NELL: So, yes. We have the one device that is decellularized. But MMM, more-than-minimal manipulation, is what we're actually classifying today. And we have the Tissue Reference Group that would determine -- so if some other process came in that was somehow different from decellularization, the TRG would look at it and make the determination as to whether or not it was considered to be more-than-minimal manipulation. If it is more-than-minimal manipulation, it would be regulated as an MMM within the CDRH, within the Center for Devices. If it were considered to not be more-than-minimal manipulation, then it would be regulated as a tissue product within CBER.

DR. PAGE: Thank you very much.

Dr. Yuh?

DR. YUH: There are a couple of reasons why I'm not as concerned about classifying this device as a Class II. I think this is somewhat of a unique situation. I mean, there's a reason why there is an *n* of 1, and it's because this is a very limited patient cohort that is not expected and I can't imagine would increase appreciably. So the notion that there'll be an influx of multiple manufacturers with different processes I think is unrealistic, and I don't think that's going to happen.

I'm comforted in the way that essentially the Class II construct has worked thus far. And it's because the company is under the ultimate regulation right now, and that's self-preservation. You know, they're working in a critical area where failure is magnified. And for example -- and to kind of illustrate the incongruity, the SG patch is basically a Class II device. But I would say that's in a critical area. It's an RVOT patch that, if there is structural failure due to the decellularization mechanism or preparation, that could lead to a sudden life-ending event as well.

So I think, you know, in this circumstance, with this device, in this scenario, in a very limited patient population that we're dealing with, that I think the system has worked so far, and I don't see a big reason, a compelling reason to change it, given the circumstances and the foreseeable future of this particular application.

DR. PAGE: Thank you, Dr. Yuh.

Dr. Somberg, and then I saw Dr. Jonas and Mr. Thuramalla.

DR. SOMBERG: I think it's appropriate to give fair balance. If a totally new decellularization process came to the fore, and there was a lot of concern about it, and it might

open the potential for new risks, FDA does not have to accept it as a 510(k) Class II device. They can say there are new risks raised. And whether this Panel or any panel says something, you are the -- determinants of that determination, and you can say we call for a PMA. Am I not right on that, Dr. Zuckerman?

DR. ZUCKERMAN: Unfortunately, it's a lot more difficult than that, to kick something out of Class II after we've established a Class II determination for the general category. The second point is Dr. Yuh's comments are quite relevant, but I do believe that there is active interest in this field. And certainly we've had reasonable success to now. But, you know, in every field that the Cardiovascular Device Division operates in, there are predominantly good actors, but there are also bad actors, and that's why we have an FDA or regulatory structure to begin with. So I do think we just need to encompass the big picture.

DR. PAGE: Thank you, Dr. Zuckerman.

Dr. Jonas?

DR. JONAS: Yes. Just to put this into context in terms of numbers, it's important for the Panel to understand there are 10 times as many adult heart surgeons as pediatric heart surgeons. Pediatric heart surgery is a really tiny field. There are lots of ventricular-assist devices for adults. Right now, there is only one for pediatric patients. And I do believe that the need for this particular valve is probably actually going to decrease in coming years. The Ross operation has gone through a phase of being very popular about 10 to 15 years ago. But the overall results and the general trend has been to decrease the number of Ross operations being done. And that's really been where a lot of pulmonary valves were being used 10 to 15 years ago. And that's an adult population requiring Ross operations.

So, if that population goes away, then we're just left with the pediatric population requiring these pulmonary valves. So we've got an actual decreasing number. So I, too, share the concern that if we make this burdensome, what would be burdensome for a manufacturer who has an adult population of many, many thousands of patients requiring heart valves is going to be quite different from what's burdensome for a manufacturer who is dealing with a very limited pediatric population. And I have not heard today any evidence that there is a difference in performance between the decellularized valve and the standard valve.

So there should at least be some consistency. The argument really has to be MM valves need to be Class III devices. And, you know, we've heard lots of people say no other heart valve is a Class II device. The fact is that the allograft MM valve is used without being a Class III device. So why should the decellularized valve, which it's really just one more manipulation of a valve that's already undergone many other manipulations? So it's inconsistent to say that the MM and the MMM should be differently labeled. They either both have to be Class III, or they both should be Class II. And I would suggest that they should be both Class II.

DR. PAGE: Well, I should mention that the MM is not the object of discussion here nor is it regulated by this -- by the CDR --

DR. JONAS: But I'm suggesting, to be consistent, it should.

DR. PAGE: Well, again, that's not our -- right now --

DR. JONAS: Okay.

DR. PAGE: -- we have the following issue. And that is how should this class of device be regulated. And let me just ask a hypothetical, since you're the person who's putting this in. Are you satisfied with the idea that if changes in location or manufacturing methodology are

changed and it is the company's decision that this does not require oversight and it is not reported, are you comfortable having that valve arrive to you to place in your patient with that level of regulatory oversight? Because that becomes the crux of the matter. It's just one of many manipulations, but it is the manipulation that really I think is at the heart of the matter, is the decellularization process. We've heard that that is proprietary. So, from one company to another, it may be different. And we also are wrestling with the issue of if it's changed, are you satisfied going forward with any other company that's supplying to you that they should self-regulate, or do you want the FDA to regulate that device that you're now going to put in your patient?

And, again, I'm taking this from the context of the assumption that this device will be available tomorrow, the next day, and so on. So we're not talking about taking the device we've discussed today off the market. But the issue comes down to, especially the surgeons, are you comfortable with that, or do you want a higher level of regulation going forward?

DR. JONAS: I can certainly understand that that would be a serious concern in the setting of a device that was highly profitable that was leading multiple companies with whom I had no long-term relationship and no understanding of their manufacturing standards. But the fact is that I don't believe that there's much profit to be made in this, which is why there's only one or two small companies that are dealing with this. And that, I believe, is why we don't have any congenital heart surgeons here or appearing arguing that this should become a Class III device. As I say, I understand that the lack of oversight might be a concern if there were multiple new companies coming into this field, but I personally, to answer your question, would not be concerned if there's one known company dealing with this.

DR. PAGE: Great. Thank you.

Dr. Thuramalla?

MR. THURAMALLA: So picking up on Dr. Page's comment that the assumption the device is not going to be taken off the market tomorrow, day after, or future, Dr. Jones from LifeNet Health brought a very important concern. If the existing system is working and if even more special controls can be put in place, disregarding this and moving to PMA is no more the least burdensome approach. And as Dr. Jones pointed out, it may be for the industry, at least a quarter -- I forget the number -- but at least a quarter million dollars extra plus regular checkups.

One other point I'd like to bring to Dr. Page's attention is, yes, the company or the industry makes the final determination on the validation, but there are other mechanisms also. For example, there is the inspection that FDA conducts on a periodical basis or in a case of an -- being reported to the FDA. Or we can also go forward and say why don't we put a special control for this particular device or a valve and have a flowchart like the FDA does in the guidance documents? If a certain thing was to change, it leads to whether it's a new 510(k) or only documentation. So that kind of mechanisms already exist in the present one.

Thank you.

DR. PAGE: Thank you, Mr. Thuramalla.

Dr. Patton?

DR. PATTON: One thing that Dr. Zuckerman mentioned was this concept of some discretion that the FDA has with respect to if this device was -- if this group of devices were classified as Class III. And this particular company, which has been having its devices implanted

for 14 years, it sounds like, and approved since 2008, with a lot of data behind it, what -- does the FDA have discretion to have a PMA that is relatively unburdensome? Like, what sort of options are there for that?

DR. ZUCKERMAN: There you go, Dr. Patton. But let's, you know, consider the broader issue, because many of you were here yesterday except for Drs. Somberg, Jonas, and Doty, and you heard Dr. Brindis make a very important plea for perhaps a increased regulation of a particular 510(k) device. You know, Dr. Brindis' comments are very useful because they stand in significant contrast to Dr. Somberg's comments and others in that the 510(k) process isn't the most user-friendly process when there is a problem or something needs to be fixed.

On the other hand, Dr. Patton, your point is an excellent one. If this is a class of devices that would be in the so-called Class III category, the Agency has a lot of discretion to interpret what is a reasonable assurance of safety and effectiveness. And we would actively encourage manufacturers, as part of our usual interactive process, to develop a doable and user-friendly type PMA submission.

I think part of your question may be inferring or asking does the sponsor right now of the presently cleared device have enough data for a PMA submission? It's a great question and probably so. And that's why I don't think that concentrating on, again, one particular sponsor is the key here. It's more how can we best make sure that we have well-functioning, important devices available to physicians and the American public within an appropriate regulatory framework such that if we need to do something special, it doesn't take two years or it's not doable and so forth.

DR. PAGE: Thank you, Dr. Zuckerman.

In a couple moments, I'm going to ask us to start addressing the questions. First, I'm going to ask Dr. Naftel who raised his hand for his comments. And then I'm going to call on Ms. McCall and Ms. Chauhan, representing patients and consumers, to see if they have any comments before we go into the question and answer period.

Dr. Naftel?

DR. NAFTEL: If I may follow up on that a little bit, we know that FDA is a pragmatic agency. The sample size in the device world is far less than the drug world, and you've dealt with that. We all have. We've seen you be so pragmatic with Berlin Heart, where you had 40 in each of two groups. So, in answer to your question, Dr. Patton, I have great faith in FDA balancing all these things and being a pragmatic agency while still performing what they're supposed to do.

We almost got what we needed this morning by the data that was presented by CryoLife. If that had been like a real postmarket study with a real hypothesis, performance goals, or whatever, we almost moved over the edge into a Class III device. We were so close. And I know I'm -- at the moment, my classification is 2.5 for the device, just you won't give me one.

(Laughter.)

DR. NAFTEL: But I think we're headed to a good place. And if it's a device Class III, there's a lot of latitude that FDA uses wisely.

DR. PAGE: Thank you, Dr. Naftel.

Ms. Chauhan, do you have any comments?

MS. CHAUHAN: I'm impressed by the ethics and integrity of the company that

presented. However, I think we're looking to the future, and we cannot assume that all companies have that same level of integrity and ethics. So I would suggest that you consider very strongly Class III.

DR. PAGE: Thank you, ma'am.

Ms. McCall?

MS. McCALL: I think the patient population that is the focus of these particular valves is a very small one. And as Dr. Jonas and Dr. Doty have mentioned, children are the focus. They're the ones that are going to get these valves. And if we can save them one surgery over the course of a lifetime, I think that's significant. And I think Dr. Jonas made almost all my good points. Thank you. So I would go with a Class II.

DR. PAGE: Thank you very much. So we very much appreciate your input as we deliberate.

At this time, I'd like to focus our discussion on the FDA questions. Copies of the questions are in your folders. I want to remind the Panel that this is a deliberation period among Panel members only. Our task at hand is to answer the FDA questions based on the data in the Panel packs, the presentations we heard this morning, and the expertise around the table. With this said, I would ask that each Panel member identify him or herself each time he or she speaks to facilitate transcription.

And I will ask for Dr. Nell to read the questions one at a time. We're not doing a vote this time, so I'm going to be looking for consensus or lack thereof from the entire Panel. We don't need to hear everybody speak on every comment. I may be looking for nods if it's a relatively easy issue. But, likewise, I do want to take these one at a time and give each question its proper

regard. We will be projecting this as well.

Dr. Nell, if you have the questions there available, you can go ahead and start reading them, and then we'll be projecting it, or I can, if you like?

DR. NELL: Question No. 1: FDA has identified the following risks to health for MMM allograft heart valves based upon literature and the Manufacturer and User facility Device Experience (MAUDE) database. The risks are as follows:

- Structural valve deterioration
- Nonstructural dysfunction
- Thrombus/ thromboembolism
- Allosensitization, rejection, or other immune responses
- Infection
- Regurgitation
- Stenosis
- Hemolysis
- Hemorrhage

a. Do you agree with the inclusion of all of these risks and the overall risk assessment of MMM allograft heart valves?

DR. PAGE: And let's go ahead through (b) as well, please?

DR. NELL: b. Do you believe that any additional risks should be included in the overall risk assessment of MMM allograft heart valves?

DR. PAGE: Thank you.

So the FDA is looking for whether you think this is sufficient or whether there is anything

to be added.

Dr. Cigarroa?

DR. CIGARROA: So I agree with all of the risks except hemorrhage. I see the process of replacing the valve as having inherent risk with hemorrhage. I don't see that in particular attributable to this valve.

DR. PAGE: Thank you.

Dr. Slotwiner?

DR. SLOTWINER: Well, I agree with the risks listed except since we might be considering tissue processing that we haven't even thought of, I don't know that this list is complete, and I'm not sure how we can make a complete list.

DR. PAGE: Well, can you perhaps posit what tissue processing problems might result in, in terms of risks to the valve?

DR. SLOTWINER: Risks to the valve or systemic. I'm sorry. If it's just the valve, then that's pretty complete, but I thought these were systemic risks as well.

DR. PAGE: Well, they kind of are, but these aren't necessarily the adverse events that result from them. For example, stroke may be an adverse event that results from embolism or thrombus.

DR. SLOTWINER: Yeah.

DR. PAGE: But any other thoughts as to -- or you're just leaving a placeholder because we can't predict the future and perhaps there might be a risk?

DR. SLOTWINER: That's really exactly my point. I mean, I just don't know what future tissue processing could bring.

DR. PAGE: Thank you.

Other comments? I'm looking around the table.

Dr. Jonas?

DR. JONAS: These valves are actually used in two different ways. They can be placed as a valve within the right ventricular outflow tract in the orthotopic position as a pulmonary valve. But most commonly they are actually used as conduits. And it's important to understand that distinction. And as a conduit, for example, constructing a connection between the right ventricle and the pulmonary arteries in a child who's been born with no main pulmonary artery, they actually do have some additional risks that are not stated here. They can become aneurysmally dilated, and that can be a true aneurysm or it can be more commonly a false aneurysm. So where the conduit is sutured to the right ventricle, we usually use a hood of pericardium or Gore-Tex, and you can get a false aneurysm at that connection point.

The more common problems that we've actually been seeing in the last few years are related to catheter intervention procedures on a conduit that a child has outgrown, and in an attempt to get an extra year or two of life out of that conduit, balloon angioplasty has been done. And there is a rupture -- there is a risk of rupture, and certainly death from hemorrhage can occur when you have a heavily calcified conduit. And with the Melody catheter-delivered pulmonary valve that's been used over the last few years, there's also a risk of rupture of the conduit as the Melody valve is implanted.

So those are some additional risks that I'd like to add.

DR. PAGE: Thank you very much for those insights.

Others?

(No response.)

DR. PAGE: So, Dr. Zuckerman, with regard -- oh, Dr. Brindis?

DR. BRINDIS: So I was wondering if our -- and I'm learning -- I feel like I'm getting CME from you today. It's really amazing.

(Laughter.)

DR. BRINDIS: Would early extirpation of the valve, would you include that for -- because that's sort of a composite of many of the risks, but need for early explantation? Would you add that?

DR. JONAS: Well, I mean, structural valve deterioration, and that includes both stenosis and regurgitation, would lead to explant, so that's a consequence of those forms of failure of the conduit or valve, yes.

DR. PAGE: Fair enough.

So, Dr. Zuckerman, with regard to Question No. 1, the list of risks is seen as valid, with the possible exception of hemorrhage, which may be a result of the procedure itself. There is also concern that we can't necessarily predict future issues. The very important additional consideration is that these are also used as conduits, at which point they may dilate either with a true or false aneurysm, and likewise, in terms of catheter balloon interventions, these can rupture and even cause death as a result of hemorrhage and rupture in patients who need further procedures, transcatheter procedures on this device.

Does this satisfactorily address the question for you, Dr. Zuckerman?

DR. ZUCKERMAN: Yes. That's been a very helpful discussion.

DR. PAGE: Thank you very much.

We'll go on to Question No. 2, please?

DR. NELL: I apologize. We are having technical difficulties. So they won't be displayed. I will just continue to read them.

Number 2: Do you agree that the device is life-supporting or presents a potential unreasonable risk of illness or injury?

DR. PAGE: And I'm going to -- I think this can be a pretty fast one in terms of even not addressing the unreasonable risk. This is one of the criteria for consideration of a Class III device. And I'm hearing from especially those who work with the device that it's life supporting. Is there anyone on the Panel who disagrees that it at least reaches the threshold of being a life-supporting device?

(No response.)

DR. PAGE: I'm seeing none. So there is concurrence about that, Dr. Zuckerman. Do we need to go into the potential unreasonable risk of illness or injury, or does this satisfactorily address the question?

DR. ZUCKERMAN: No. I think we're ready to go to Question 3.

DR. PAGE: Great. Thank you.

Let's read Question 3, please?

DR. NELL: Question No. 3: FDA believes that insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness of MMM allograft heart valves. Given the relative novelty of MMM processing and limited availability of clinical data, as well as the limitations of those data (specifically, only 1 cleared MMM allograft heart valve, no randomized control studies, and small

patient numbers), it is challenging to draw conclusions regarding the safety and effectiveness of MMM allograft heart valves, particularly regarding their long-term performance, immunogenicity, and potential for recellularization and/or host adaptation. Consequently, FDA does not believe that special controls can be established to mitigate the known risks to health associated with these devices.

a. Do you agree with this assessment?

b. If you disagree with this assessment, please identify the information you find sufficient to support a reasonable assurance of safety and effectiveness of MMM allograft heart valves when intended for use in heart valve replacement procedures.

c. In addition, please identify the special controls that could be established that you believe would be sufficient to mitigate the risks to health and provide a reasonable assurance of safety and effectiveness of MMM allograft heart valves intended for use in heart valve replacement procedures.

DR. PAGE: Thank you.

I'm going to try to frame this in the following way. We've discussed the issue that no matter where we go with the next two questions, that we're assuming the device will be available and that the FDA will work with the manufacturer to identify the least burdensome way to have a flexible PMA to maintain availability of the device we've been talking about today. So I do want to hear people's voice on that, but frankly, if this becomes Class II, then that discussion doesn't need to take place.

Also, this becomes very easy for those who agree with the assessment. You're just answering (a). But for those who disagree, I will want them to, at least the first people

speaking, to address (b) and (c). And then I'll ask for others to weigh in and amplify or expand on the comments made. But we don't need to repeat every perspective if the comment has already been made. But I do really want to hear from just -- from everybody in the Panel in terms of this.

I see Dr. Cigarroa and Dr. Furie?

DR. CIGARROA: So although I am comfortable with the device and the data that was presented today, I think it becomes very challenging to understand in the future what the market and the number of valves and the clinical scenarios in which they might be implanted that undergo a decellularization technique, however that might evolve in the future. And, therefore, I think that the importance of the PMA process with both preapproval inspection and the postmarket mandatory, obligatory processes are important in this situation. And, therefore, I support the FDA's assessment.

DR. PAGE: Dr. Furie and then Dr. Somberg?

DR. FURIE: Thank you.

I don't agree with this assessment because I believe that the collaboration between CryoLife and the FDA and the data presented today demonstrate that the special controls that have been put in place are actually very impressive. And I agree with Dr. Somberg that it seems to be an example of a system that's worked.

However, I also believe that the differential here is between special controls that are voluntary and a reporting structure which is dependent upon the specific company's discretion as opposed to something that's standardized and mandatory.

DR. PAGE: I'm not sure I understood about the issue of the voluntary versus mandatory

reporting. Were you saying that mandatory reporting should be part of the special controls in a Class II?

DR. FURIE: No, as part of a Class III in that it's very hard to anticipate in the future whether other companies or other procedures will require greater oversight, and so as a result, I think the mandatory component becomes essential.

DR. ZUCKERMAN: Okay. So, Dr. Furie, you've made several very important points, but it's really important to understand the nomenclature here. You've been impressed that there's been good scientific interchange between one company, CryoLife, and the FDA. But special controls are different. They refer to guidance documents for specific areas such that regardless of any company that approaches the FDA, they could refer to these special controls and know what to do. And I think the point that Dr. Nell has been helping us with is that while for a particular device with lots of proprietary information, a regulatory agency has figured out what to do, for the broader landscape, given that n=1, we have limited knowledge of this area. The development of these guidance documents by experts such as Dr. Nell is very difficult to conceive. And that's why we do not technically have special controls right now.

DR. PAGE: So I guess, Dr. Furie, I heard a disagreement with the assessment, but you subsequently said that you felt that mandatory oversight was necessary. So were you jumping forward to what class you would be putting this into?

DR. FURIE: Perhaps I'm jumping ahead.

DR. PAGE: Okay. And may I ask what class just so I understand the context of how important you think that issue is?

DR. FURIE: I think it's important enough to warrant Class III.

DR. PAGE: Okay. Thank you very much.

Dr. Somberg?

DR. SOMBERG: Well, I think I've stated -- for the current of brevity, I don't want to restate in a long way, but I do think the system has worked. I do believe that it should remain a Class II. I think there would be ability for the FDA to mandate, as they have in this -- with one specific case -- that the 510(k) have clinical data in its presentation, that there be -- they could mandate that there would be a postmarketing study. And there also could be a mandated that there be a notification of any change in manufacturing. So, if the special controls, which there are special controls out there requiring durability testing, the mechanical things we saw with those different clips and all that, for tissue integrity and that sort of thing, and if -- and we've been talking about changing the decellularization process. If that changes, then you can mandate notification. And then if someone comes up with some hair-brained, outside-of-the-ballpark idea, FDA can reconsider what they may concern. But I don't see that as an immediate possibility, and therefore, to do things on a theoretical basis, in my opinion, is wrong.

DR. PAGE: Thank you.

Others on the Panel? Dr. Jonas?

DR. JONAS: Addressing Question 3(b), what information do I find --

DR. PAGE: I'm sorry. We're still on all 3(a), (b), and (c). So can you give us your answer to (a) first?

DR. JONAS: (a), I do not agree with the assessment --

DR. PAGE: No, good.

DR. JONAS: And the reason that I feel there is sufficient information to assure safety and

effectiveness of the MMM allograft heart valve is that, certainly, my own search of the literature, as well as the search of the literature that I heard here this morning, really has not identified a single review that suggests that the decellularized valve performs in an inferior fashion to the standard allograft valve. I believe Dr. Brown's series is a large series and that if there were going to be a serious problem with the MMM valve, that series would have identified some difference in function between the decellularized valve and the standard allograft valve.

DR. PAGE: Great. Thank you.

Dr. Lange?

DR. LANGE: I appreciate the fact that the company has a very good product, and all of us want to keep it on the market. We have a new company that's putting a new valve in, and if I handed it to you today, Dr. Jonas, would you be willing to use that valve and say it's equally as effective?

DR. JONAS: Well, I'd need a little more information.

DR. LANGE: Exactly. That's my point. That's why I think it requires Class III. In other words, I think it needs to go through a certain scrutiny both premarketing and -- as well to make sure that if there's -- if that process changes as well, that it doesn't somehow interfere with the product. We had the same thing when we looked at the AICDs, when there were changes from the manufacturer that the manufacturer didn't report because they didn't think it was substantial. And it resulted in a substantial number of those products not functioning properly. So I agree with my colleague, Dr. Naftel. I have great confidence in the FDA making it as least onerous as possible, but having the flexibility to make sure that the products we put in kids or

adults are safe.

DR. PAGE: Thank you, Dr. Lange.

And if people want to speak to Question 4, they may, especially if it fits with their comments, but we are on number 3, and I will go through No. 4 to just get an idea of everybody in the Panel with a relatively simple discussion.

Dr. Hirshfeld, of course?

DR. HIRSHFELD: Thank you. Just two very brief comments. First of all, I think in the interest of consistency, because all other heart valves are regulated as Class III devices, and this is, in part, because we know there are major engineering and major material science issues with other heart valves that have been responsible for this persistence of these devices being in Class III, these are devices that don't really have engineering challenges so much as they have biological manipulation challenges, which I think are at least equivalently complex. And so, therefore, I think that it makes sense to have this complex a series of devices being in Class III.

The second thing is that the FDA slide that showed the difference in terms of the FDA's regulatory authority between a Class III and a Class II device I thought was compelling, not so much because maybe the FDA might have an issue with the performance of the currently marketed device, but as has been mentioned, if other companies get into the business and are not performing at the same level, the FDA would, you know, be able to use that authority that's provided by Class III.

DR. PAGE: So I am hearing your response to Question 4 as to classification. So was your response to (a) no, 3(a)? Do you agree with the --

DR. HIRSHFELD: Yes.

DR. PAGE: Or --

DR. HIRSHFELD: 3(a) was no. It really sort of an expansion --

DR. PAGE: No, but -- I'm sorry.

DR. HIRSHFELD: No, 3(a) was yes --

DR. PAGE: You would agree --

DR. HIRSHFELD: I'm sorry.

DR. PAGE: So you were affirmative to 3(a)?

DR. HIRSHFELD: Yes.

DR. PAGE: Thank you very much, sir.

DR. HIRSHFELD: Yeah, okay.

DR. PAGE: Who else would like to speak or shall I call on people?

(No response.)

DR. PAGE: Does anybody -- do people feel that they've had an opportunity to voice their perspectives? I would like to just hear a yes or a no, if nothing else, from the Panel on Question 3(a) anyway.

Dr. Slotwiner?

DR. SLOTWINER: Yes. I think it's important not to be distracted by the good example we have here at hand but to think of the 30,000-foot level. And so I agree with the FDA's assessment.

DR. PAGE: So 3(a) is a yes?

DR. SLOTWINER: Yes.

DR. PAGE: And Dr. Ohman?

DR. OHMAN: I agree.

DR. PAGE: And Dr. Cassiere?

DR. CASSIERE: 3(a), I'd have to say a yes.

DR. PAGE: And Dr. Doty?

DR. DOTY: I'm going to say, no, I disagree with the FDA assessment.

DR. PAGE: And do you want to expand in terms of 3(b) or (c), or do you agree with what's already been said?

DR. DOTY: I agree mostly with what's been said. I think the special controls are in place to keep it in Class II.

DR. PAGE: Thank you.

And Dr. Hirshfeld I've heard from.

Dr. Yuh?

DR. YUH: I disagree. I think that the notion of the decellularization is more of a distinction without a difference, quite frankly, in comparison to all of the other manipulations that are afforded on these valves. You know, I think in response to Dr. Lange's, you know, very good question, is if a company, you know, presented me with a new valve, with a new technique of decellularization, would I use it, and the answer would be no unless that company could convince me that this was superior to the existing valve. They would, in effect, be forced by market forces to come up with comparable data especially in this, you know, critical population. So, you know, whether that's by design or not, the current construct right now, I think, works for that reason. That's the only thing I really have to add to that question.

DR. PAGE: Thank you, Dr. Yuh.

Dr. Brindis?

DR. BRINDIS: So my answer is somewhere between yes and no, and the reason why that is, I think going forward with new devices, they don't have processes in place, but with the retrospective scope of the data presented related to the product on the market, I have reasonable assurance related to that.

DR. PAGE: Fair enough. And we'll come back to you as we go through Question 4.

Dr. Naftel?

DR. NAFTEL: I agree with what Dr. Brindis just said. It's perfect.

DR. PAGE: Dr. Kandzari?

DR. KANDZARI: I'm the third in agreement. I think that if this were an assessment of the two companies presented today and we knew that that was going to exist in perpetuity, then we might have a different assessment of special controls, but not knowing the future of this technology and its evolution, I agree.

DR. PAGE: So that was agreeing with 3(a). Thank you very much.

Dr. Patton?

DR. PATTON: I also agree. And I wanted to speak to what Dr. Yuh just said with respect to the fact that we are making these decisions for -- not just having to take into consideration that other companies may come up with other products, but other physicians may also respond to the offering of a device on the market without as much scrupulous care to attention to data as Dr. Yuh would have. And I think that's important with respect to patient safety as well.

DR. PAGE: Thank you.

And, Dr. Somberg, we've already heard from you.

Are there any other comments from the Consumer, Industry, or Patient Representatives?

(No response.)

DR. PAGE: Okay.

So, Dr. Zuckerman, in general, I'm hearing I believe a majority of the Panel feeling that the answer to (a) is affirmative. We have a couple yes/noes here. Those who disagree with that statement are basing that on the fact that problems have not been seen. And I think we're all here impressed by CryoLife's data, their presentation, their quality, I think their patient-centeredness. And that's swaying individuals, including a couple of people who have the opportunity to put in these devices, which means a lot to us. But, nevertheless, I'm seeing more yeses to 3(a) than noes, and I think we've addressed why the noes are saying no based on Questions 3(b) and (c).

Does this adequately address the question, Dr. Zuckerman?

DR. ZUCKERMAN: It does for me.

Dr. Nell, do you have any follow-up question here?

DR. NELL: No, no additional questions.

DR. PAGE: Great. Thank you.

We have the last question, and then I am going to ask for people as they give their response to -- if it's already been said, I don't think they need to say it, but I would like people to comment on their feeling about the device that's on the market and the need for that device to be available if they think that's the case, because that's something that I know the FDA would value in terms of moving forward and finding the least burdensome way to a PMA and approval

as a Class III device if we got there.

So, at this point, why don't we read Question 4?

DR. NELL: Question 4: FDA believes that MMM allograft heart valves should be classified as Class III. Please indicate whether you agree with FDA's proposed classification. In accordance with 21 C.F.R. 860.93, if you recommend a classification other than Class III for this device, please discuss the reasons for your recommendation.

DR. PAGE: Thank you very much.

Why don't we start at this side of the room first with Dr. Somberg, and again, if you care to comment, especially if you're voting for III, I think we need to comment, but likewise, what swayed you to your vote or your perspective and recommendation one way or the other.

So Dr. Somberg?

DR. SOMBERG: I think you've heard my perspective. I'm not sure I want to repeat it again, but I don't agree with that.

DR. PAGE: Great. So you would continue in Class II for the reasons you've already stated.

Dr. Patton?

DR. PATTON: I agree with Class III. I think that if implanted heart valves aren't Class III devices overall, what would be? I do also suspect that CryoValve has met all of the sort of requirements that we usually look for in recommending approval for PMA device. It's clearly a device that the cardiac surgeons in the room have been strongly supportive of as playing an important role in patient care.

DR. PAGE: Thank you.

Dr. Kandzari?

DR. KANDZARI: Again, for the reasons I, I think, mentioned in the previous discussion, I would vote for Class III, although I would hopefully encourage FDA to consider that the existing technologies may have sufficient information forthcoming already at hand to support the PMA without additional burdensome study.

DR. PAGE: Thank you.

Dr. Naftel?

DR. NAFTEL: I agree with Class III classification, and I agree with the last two speakers about hoping FDA is humane.

(Laughter.)

DR. PAGE: Thank you.

Dr. Brindis?

DR. BRINDIS: I also agree that it's a Class III indication. And I know the FDA is humane. And if they're asking and feeling that Class III indication is a way to assuring safety and efficacy in going forward for the people in the United States and people who look outside of the United States at what we're doing, then I think we should support that.

DR. PAGE: Thank you.

Dr. Furie?

DR. FURIE: I also agree with a Class III recommendation and hope that a way can be found to help this remain on the market in the least burdensome way possible.

DR. PAGE: Thank you.

Dr. Lange?

DR. LANGE: I'd vote for Class III as well, and my previous colleagues have summarized the reasons why very well.

DR. PAGE: Thank you.

Dr. Yuh?

DR. YUH: Obviously, I disagree with the Class III classification. I think that, you know, the least burdensome way or the least onerous way, or however you want to put it, is unlikely to produce the kind of data and the quality of data, given the small patient cohort, that's going to satisfy, or actually, supersede the data that's already been collected and likewise satisfy a Panel like this. So, you know, I trust that the FDA will make every effort -- would make every effort, but I just -- I'm not sure how that would happen.

DR. PAGE: Thank you.

Dr. Hirshfeld?

DR. HIRSHFELD: I agree with Class III. I think all my feelings have already been articulately stated. I would just add, whether or not it's appropriate at this point, that I wonder whether or not there should be a mechanism to bring MM valves under the purview of CDRH.

DR. PAGE: Thank you. That will be in the record and will be addressed as appropriate by the regulatory bodies, I'm sure.

(Laughter.)

DR. PAGE: Dr. Doty?

DR. DOTY: I disagree with Class III. I favor keeping it in Class II, and you've heard my opinions.

DR. PAGE: Thank you.

Dr. Cassiere?

DR. CASSIERE: I agree with the Class III, and I think there's enough data presented, even though it's not non-peer-reviewed and non-FDA-reviewed, that it will pass the PMA process eventually.

DR. PAGE: Thank you.

Dr. Jonas?

DR. JONAS: I vote for Class II. And, once again, just to emphasize, this is truly a life-saving conduit. The smallest alternative that is available to us is a 12 mm diameter Contegra bovine jugular conduit. There is no smaller conduit available. There just isn't anything else. So we have to have these devices available.

DR. PAGE: Thank you very much.

Dr. Ohman?

DR. OHMAN: I vote for Class III. And I would also like to say that this discussion would have been dead easy if CryoLife hasn't done such a good job of actually providing data. So it would have been just a very abstract discussion, which would have been easier to go through. I do hope that everybody recognized that what you've actually seen using the 510(k) process with the FDA really worked well. It provided actually a lot of insight into this. But going forward in the future, we really cannot predict what's going to happen, and therefore, I think it has to stay a Class III.

DR. PAGE: Thank you.

Dr. Cigarroa?

DR. CIGARROA: So I, too, agree with Class III. That said, caring for patients with

congenital heart disease and seeing a fair number of individuals who have conduits and implanting Melody valves, I would congratulate CryoLife on bringing to market an outstanding product that makes a substantial difference for many patients, and believe that it should remain on the market through the process. I'm convinced that the FDA will. However, that doesn't ensure that the regulations associated with Class II designation would predict the same outcome for other manufacturers.

DR. PAGE: Thank you very much.

And Dr. Slotwiner?

DR. SLOTWINER: I agree with Class III for the reasons that have been said already and echo my colleagues who strongly wish the FDA will work with the sponsor to make sure this valve continues to be available.

DR. PAGE: So, Dr. Zuckerman, if I may summarize. And with a straw vote, I see four in favor of classification as Class II and 11 in favor of Class III. I'll weigh in myself. And while I have great respect for the Industry Representatives here and applaud them on their presentation and, more important, on them providing really life-saving, life-sustaining valve and conduit therapy to some of our most needy patients, from a regulatory standpoint, I think we must have a higher level of regulation. And as such, I would favor Class III for these devices.

That being said, I'll look around and see if anybody doesn't agree we want these devices to be available and for the FDA to work closely with the CryoLife people to make this, as you said, and I'll quote, "the least burdensome path possible" for the PMA process to be undertaken and for this technology, this device, to be available to patients who need it. Going forward, though, I trust in the regulatory process, that because of the stakes here, that a level of

oversight consistent with Class III PMA is necessary.

Have we adequately addressed the questions that you have for us, Dr. Zuckerman?

DR. ZUCKERMAN: Yes, you have.

Before we end, Dr. Nell, do you have any follow-up questions?

DR. NELL: No, I have no further questions.

DR. ZUCKERMAN: Okay. So this has been extremely helpful for FDA, and I do think one of the key parts of this meeting was just the discussion about the need for this device. And, certainly, FDA will really be mindful of that discussion.

Thank you.

DR. PAGE: Thank you.

Before we adjourn, I do want to look to Mr. Thuramalla, Ms. McCall, and Ms. Chauhan as to whether you have any other further comments for the Panel?

Mr. Thuramalla?

MR. THURAMALLA: So, in closing, I'd like to present that from an industry perspective and for the reasons pointed out by Dr. Somberg, Dr. Yuh, Dr. Doty, Dr. Jonas, and others, the existing system of a Class II 510(k) route works. This can be further improved by adding special controls, including mandated process controls and follow ISO standards and other related to make sure enough regulated oversight is imposed.

Lastly, as some of the Panel members and clinical experts indicated, they're comfortable with the present device. And in the spirit of the least burdensome approach, the current classification should not be changed, and this could make it much more burdensome, and this could bring in a potential risk that the device may not be available.

Thank you.

DR. PAGE: Thank you. And I hope you know we take your sentiments and especially those four people that you mentioned who advocated a classification of Class II, we take those comments very seriously.

Ms. Chauhan?

(No response.)

DR. PAGE: Thank you. As always, we appreciate your participation.

Ms. McCall?

(No response.)

DR. PAGE: Okay. Well, with that, I want to thank the Panel and the FDA and the Industry Representatives and the people who spoke up in the open public comment for their participation. I remind everyone we're here to do the best we can for the United States public, for our patients, and for the physicians who are caring for them. And I really appreciate how seriously everybody took this deliberation and your efforts both in advance of the meeting and during this meeting.

Unless, Dr. Zuckerman, you have any final comments -- I'm seeing no -- then, as such, the October 9th, 2014 meeting of the Circulatory System Device Panel is now adjourned. Thank you very much. Safe travels.

(Whereupon, at 12:36 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

CIRCULATORY SYSTEM

October 9, 2014

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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Official Reporter

Free State Reporting, Inc.
1378 Cape St. Claire Road
Annapolis, MD 21409
(410) 974-0947